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#### IN THE CLAIMS

1. (Currently Amended) A method of synthesis of a chemical compound having the formula A-B-C

where the A is a chemiluminescent moiety comprising a phthalhydrazide,

B is an energy acceptor moiety, and

C is a biologically active moiety

comprising the steps of

forming a benzophenone,

forming a diaryl ethylene, and

performing comprising the steps of at least one of

- (a) forming benzophenone;
- (b) forming a diaryl ethylene;
- (c) attaching a precursor to generate a phthalhydrazide; such as phthalimide, aminophthalic acid diester, aminophthalic acid dihydrazide, aminophthalic anhydride and phthalhydrazide protected by a hydrolyzable group to form the precursor-ethylene conjugate, and
- (d) condensing two ethylene-precursor conjugates to form a precursor-pentadiene conjugate; , and
- (e) (b) condensing two diaryl ethylene to form a pentadiene;, and
- (f) attaching a precursor to <u>a pentadiene</u> generate a phthalhydrazide such as phthalimide, aminophthalic acid diester, aminophthalic acid dihydrazide, aminophthalic anhydride and phthalhydrazide protected by a hydrolyzable group, to form <u>a</u> the precursor-pentadiene conjugate; and
- (g) converting the <u>a</u> precursor to the phthalhydrazide by at least one of the corresponding reactions

phthalimide with hydrazine,

aminophthalic acid diester with hydrazine,

aminophthalic anhydride with hydrazine, and

hydrolysis of phthalhydrazide protected by a hydrolyzable group to form a carrier compound, and

reacting the carrier compound with the biologically active moiety to form a corresponding conjugate.

2. (Original) The method of synthesis of the compound of claim 1 wherein the compound

serves to delivery the C moiety to a desired biological compartment.

- 3. (Original) The method of synthesis of the compound of claim 1 wherein the compound is a prodrug.
- 4. (Original) The method of synthesis of the compound of claim 3 wherein the compound serves as a prodrug for at least one of antiviral agents for the treatment of viral infections and anticancer agents for the treatment of cancers.
- 5. (Original) The method of synthesis of the compound of claim 4 wherein the compound serves as a prodrug for the treatment of at least one of the group of viruses comprising Human Immunodeficiency Virus (HIV), herpes viruses such as Herpes Simplex Virus, (HSV), Epstein-Barr Virus (EBV), Varicella Zoster (VZV), Cytomegalovirus (CMV), HSV-6, and HSV-8 (Kaposi's sarcoma), Human Papilloma Virus (HPV), rhinoviruses, and hepatitis-linked viruses.
- 6. (Original) The method of synthesis of the compound of claim 4 wherein the compound serves as a prodrug for the treatment of at least one of the group of cancers comprising colon, breast, lung, renal, retinal, and skin.
- 7. (Original) The method of synthesis of the compound of claim 3 wherein the prodrugs have increased bioavailability.
- 8. (Original) The method of synthesis of the compound of claim 2 wherein the compound is a cellular permeant prodrug.
- 9. (Original) The method of synthesis of the compound of claim 8 wherein intracellular drug release occurs when the prodrug reacts with cellular free radicals via a mechanism involving chemiluminescence, photochromism, and intramolecular energy transfer.
- 10. (Original) The method of synthesis of the compound of claim 1 wherein the C moiety is a pharmaceutical agent or drug.
- 11. (Original) The method of synthesis of the compound of claim 10 wherein the pharmaceutical agent is at least one of the group of antilipidemic drugs, anticholesterol drugs, contraceptive agents, anticoagulants, anti-inflamatory agents, immuno-suppressive drugs,

antiarrhythmic agents, antineoplastic drugs, antihypertensive drugs, epinephrine blocking agents, cardiac inotropic drugs, antidepressant drugs, diuretics, antifungal agents, antibacterial drugs, anxiolytic agents, sedatives, muscle relaxants, anticonvulsants, agents for the treatment of ulcer disease, agents for the treatment of asthma and hypersensitivity reactions, antithroboembolic agents, agents for the treatment of muscular dystrophy, agents to effect a therapeutic abortion, agents for the treatment of anemia, agents to improve allograft survival, agents for the treatment of disorders of purine metabolism, agents for the treatment of ischemic heart disease, agents for the treatment of opiate withdrawal, agents which activate the effects of secondary messenger inositol triphosphate, agents to block spinal reflexes, and antiviral agents including a drug for the treatment of AIDS.

- 12. (Original) The method of synthesis of the compound of claim 1 wherein the C moiety is released by an oxidation reduction reaction with the target cell's electron carriers or by reaction with free radicals produced as a consequence of electron transport.
- 13. (Original) The method of synthesis of the compound of claim 12 wherein the C moiety is released into a desired compartment in active form.
- 14. (Original) The method of synthesis of the compound of claim 13 wherein the released C moiety has a greater therapeutic effect or therapeutic ratio relative to the free C agent alone.
- 15. (Original) The method of synthesis of the compound of claim 14 wherein the released C moiety has a greater therapeutic effect or therapeutic ratio relative to the free C agent alone as a consequence of at least one of altered pharmacokinetics or pharmacodynamics such as a desirable kinetics of release, a resistance to inactivation or excretion, greater solubility, enhanced absorption, a diminished toxicity, or greater access to the cellular or biological compartment which is the site of action of C.
- 16. (Original) The method of synthesis of the compound of claim 1 wherein A represents a functionality which undergoes at least one of

an oxidation reduction where electrons are transferred directly between A and the target cell's electron carriers, and

a reaction with free radicals of oxygen which are produced as a consequence of electron transport

such that an excited state is produced in A as a consequence of its participation in one of

these reactions.

- 17. (Original) The method of synthesis of the compound of claim 16 wherein A undergoes intramolecular energy transfer from its own excited state to the B functionality which is an energy acceptor.
- 18. (Original) The method of synthesis of the compound of claim 17 wherein upon receiving energy from A, B achieves an excited state which relaxes through heterolytic cleavage of the covalent bond of B with C where C is a drug moiety which is released into the environment.
- 19. (Original) The method of synthesis of the compound of claim 18 wherein the released drug molecule effects a therapeutic functional change by a mechanism which comprises receptor mediated mechanisms including reversible and irreversible competitive agonism or antagonism including a molecule known as a suicide substrate or a transition state analogue mechanism or a noncompetitive or uncompetitive agonism or antagonism or the action is by a nonreceptor mediated mechanism including a "counterfeit incorporation-mechanism".
- 20. (Currently Amended) The A method of synthesis of a chemical the compound of claim 1 having the formula A-B-C

where wherein the A is a chemiluminescent moiety;

B is an energy acceptor moiety, and

C is a biologically active moiety

the method comprising the steps of condensing A and B to form a conjugate A-B and reacting the conjugate A-B wth C wherein the chemiluminescent moiety comprises a molecule selected from comprises at least one of the group consisting of

molecules undergoing reaction involving peroxides and oxygen free radicals,

molecules undergoing reaction involving oxidation or reduction, and

molecules undergoing both reaction with peroxides and oxygen free radicals followed by an oxidation or reduction reaction.

21. (Original) The method of synthesis of the compound of claim 20 wherein the chemiluminescent molecule comprises at least one of the group of luminol and its derivatives, lucigenin and its derivatives, Lophine and its derivatives, acridinium esters and acridans, tetraphenylpyrrole, phthalhydrazides, acyloins, biacridinium salts, vinylcarbonyls, vinylnitriles, tetrakis (dimethylamino) ethylene, acylperoxides, indoles, tetracarbazoles and active oxalates.

- 22. (Original) The method of synthesis of the compound of claim 20 wherein the chemiluminescent molecule comprises at least one of the group of ruthenium chelates 2, 6-diaminopyrene, or cation radicals and molecules which follow a Chemically Initiated Electron Exchange Luminescence mechanism such as certain dioxetans and dioxetanones.
- 23. (Original) The method of synthesis of the compound of claim 20 wherein the chemiluminescent molecule comprises at least one of the group of dioxene derivatives and other compounds that form a dioxetan by reaction with superoxide and then produce efficient chemiluminescence by a CIEEL mechanism.
- 24. (Curently Amended) The method of synthesis of the compound of claim 20 wherein the chemiluminescent molecule comprises at least one of the group of

2,6-diaminopyrene 
$$\begin{array}{c} NH_2 \\ \hline \\ NH_2 \\ \hline \\ NH_2 \\ \hline \\ NH \\ NH \\ \hline \\ NH \\ NH \\ \end{array}$$

Dioxene

$$O$$
 $R_1$ 
 $R_1$ 

Imidazole derivatives

$$R_1 \stackrel{N}{\longleftarrow} R_2$$

Sulfonyloxamides

Indole derivatives

Tetrakis(dialkylamino)ethylene

2,5,7,8-tetraoxabicyclo-[4.2.0.] octane

$$O$$
 $O$ 
 $R_2$ 
 $R_1$ 
 $O$ 
 $O$ 

Dioxetan

$$0-0$$
 $R_1$ 
 $R_2$ 
 $R_3$ 

Lucigenin

Lophine Acridinium esters Active oxalate Tris-2,2'-bipyridinedichlororuthenium (II) Dioxetanone Dipheyl peroxide

- 25. (Currently Amended) The method of synthesis of the compound of claim 1 20 wherein the energy acceptor moiety B moiety is a photochromic compound.
- 26. (Original) The method of synthesis of the compound of claim 25 wherein the

photochromic compound comprises one which demonstrate photochromic behavior with electromagnetic radiation and bleaching agents.

- 27. (Original) The method of synthesis of the compound of claim 26 wherein the A functionality is chemiluminescent, and the B functionality is such that the photodissociative drug release spectrum of B overlaps the chemiluminescence spectrum of A.
- 28. (Original) The method of synthesis of the compound of claim 25 wherein the photochromic compound comprises a cationic dye.
- 29. (Original) The method of synthesis of the compound of claim 28 wherein the cationic dye comprises at least one of a di and triarylmethane dyes, triarylmethane lactones and cyclic ether dyes, cationic indoles, pyronines, phthaleins, oxazines, thiazines, acridines, phenazines, and anthocyanidins, and cationic polymethine dyes and azo and diazopolymethines, styryls, cyanines, hemicyanines, dialkylaminopolyenes, and other related dyes.
- 30. (Currently Amended) The method of synthesis of the compound of claim 28 wherein the cationic dye comprises at least one of

Malachite Green	42000
Helvetia Green	42020
Basic Blue 1	42025
Brilliant Blue	
Setoglaucine	
Basic Green 1	42040
Brilliant Green	
Acid Blue 1	42045
Xylene Blue VS	
Patent Blue V	
Alphazurine 2G	
Acid Blue 3	42051
Brilliant Blue V	
Patent Blue V	
Food Green 3	42053

Serial No. 10/828,558 Page 10 of 125

FDC Green 3	
Acid Green 6	42075
Light Green SF Bluish	
Acid Blue 7	42080
Xylene Blue AS	
Patent Blue A	
Acid Green 3	42085
Acid Blue 9	42090
Erioglaucine	
Acid Green 5	42095
Light Green SF Yellowish	
Acid Green 9	42100
Erioviridene B	
Acid Blue 147	42135
Xylene Cyanol FF	
Basic Red 9	42500
Pararosaniline	
Basic Violet 14	42510
Fuchsin	
Magenta	
Basic Fuchsin	42510B
Basic Violet 2	42520
New Magenta	
Hoffman Violet	42530
Iodine Violet	
Basic Violet 1	42535
Methyl Violet	
Basic Violet 13	42536
Methyl Violet 6B	
Basic Violet 3	42555
Crystal Violet	
Gentian Violet	
Iodine Green	42556
Basic Blue 8	42563
Victoria Blue 4R	

Serial No. 10/828,558 Page 11 of 125

Acid Blue 13	42571
Fast Acid Violet 10B	
Acid Blue 75	42576
Eriocyanine A	
Methyl Green	42585
Ethyl Green	42590
Basic Violet 4	42600
Ethyl Violet	
Acid Violet 49	42640
Wool Violet 5BN	
Acid Blue 15	42645
Brilliant Milling Blue B	
Acid Violet 17	42650
Acid Violet 6B	
Wood Violet 4BN	
Formyl Violet	
Acid Violet 5BS Conc.	
Acid Violet 19	42685
Acid Fuchsin	
Red Violet 5R	42690
Acid Blue 22	42755
Aniline Blue	
Soluble Blue	
Solvent Blue 3	42775
Solvent Blue 3	42780
Methyl Blue	
Aurin	43800
Mordant Blue 3	43820
Eriochrome Cyanine R	
Acid Green 16	44025
Naphthalene Green V	
Pontacyl Green NV Extra	
Basic Blue 11	44040
Victoria Blue R	
Basic Blue 15	44085

Serial No. 10/828,558 Page 12 of 125

Night Blue

Acid Green 50

44090

Wool Green S

Kiton Green S. Conc.

Basic Green 3

Sevron Green B

Brilliant Blue F & R Extra

Brilliant Green Sulfonate

Hexakis (hydroxyethyl)

New Green

$$(CH_3)_2N$$
  $C^*$   $COCH_2$ 

Phenolphthalein

Malachite Green Ethiodide

$$(CH_3)_2N$$
  $C^+$   $N(CH_3)_2C_2H_5$ 

Hydroxyalkylated Pararosanilines

### Serial No. 10/828,558 Page 13 of 125

Hydroxyalkylated New Fuchsins

New Yellow

$$(CH_3)_2N$$
  $C^*(C_6H_5)_2$ 

Doebner's Violet

$$H_2N$$
  $C^*C_6H_5$ 

New Red

$$(CH_3)_2N$$
  $C^*$   $C_6H_5$   $CH_3$ 

Bis(hydroxyethyl) Doebner's Violet

"New Magenta"

Tetrakis(hydroxyethyl) Doebner's Violet

$$\left[ (HOCH_2CH_2)_2N - \right]_2 C^*C_6H_5$$

Trichloro Crystal Violet

#### Serial No. 10/828,558 Page 15 of 125

Slow Red

$$(CH_3)_2N \longrightarrow C^3 \longrightarrow CCH_3$$

$$(C_3H_7NH \longrightarrow C^4 \longrightarrow C^4 \longrightarrow CH_3$$

$$(CH_3)_2N \longrightarrow C^4 \longrightarrow CH_3$$

$$(CH_3)_2N \longrightarrow C^4 \longrightarrow CH_3$$

$$(C_2H_5)_2N \longrightarrow C^4 \longrightarrow C^4$$

$$(CH_3)_2N \longrightarrow C^* \longrightarrow CCH_3$$

$$(CH_3)_2N \longrightarrow C^* \longrightarrow CCH_3$$

$$(CH_3)_2N \longrightarrow C^* \longrightarrow F$$

$$(CH_3)_2N \longrightarrow C^* \longrightarrow N(CH_3)_2$$

<sup>a</sup> Only the cyanide, bisulfite, and hydroxide ions are considered, regardless of the other anions present in the solution.

<sup>&</sup>lt;sup>b</sup> More detailed descriptions of the compositions of photochromic materials tested are given in Macnair's review [255; tables 1A-4].

<sup>&</sup>lt;sup>c</sup> Ethanol.

<sup>&</sup>lt;sup>d</sup> Diethyl ether.

<sup>&</sup>lt;sup>e</sup> 1,2-Dichloroethane.

f 1,1-Dichloroethane, cyclohexane-1,1-dichloroethane, or cyclohexane-1,2-dichloroethane mixtures.

g Benzene.

- <sup>h</sup> Dimethylsulfoxide, neat and aqueous.
- i Acetone.
- JACETIC ACID.
- <sup>k</sup> Ethyl acetate.
- <sup>1</sup> Ethyl bromide.
- <sup>m</sup> 2-Methoxyethanol.
- <sup>n</sup> Chloroform.
- <sup>o</sup> Ethanol with KCN.
- <sup>p</sup> Ethanol wiih KOH.
- <sup>q</sup> Carboxylic acids-acetic to stearic; hydrocinnamic acid; ethyl and butyl acid phthalates.
- Octadecylnitrile, tributyl phosphate, aniline, 2-(p-tert-butylpheno xy)ethanol, tetraethyleneglycol dimethyl ether, or poly(ethylene glycols).
- <sup>s</sup> Amides-formamide to stearamide; methylformamide or methylacetamide; dimethyl- or diethyl-formamide or acetamide.
- <sup>t</sup> Three-to-one solutions of cellulose acetate with any of the following five-to-one plasticizer mixtures: butyl stearate, Polyethylene Glycol 600-butyl acetoxystearate, butyl stearate, or Dowanol EP-butyl acetoxystearate.
- <sup>u</sup> Water containing SO<sub>2</sub>.
- <sup>v</sup> Water containing bisulfite and papain.
- <sup>w</sup> Poly(vinyl alcohol) with dimethylsulfoxide (5:1).
- <sup>x</sup> Films, containing residual solvent, cast from the following solutions: ethanol-acetone solutions of vinyl acetate-vinyl alcohol copolymer; aqueous poly(vinyl alcohol); aqueous poly(vinyl pyrrolidone); or aqueous methyl vinylether-maleic acid copolymer.
- <sup>y</sup> Methanol-dioxane with aqueous NH<sub>4</sub> HSO<sub>3</sub>.
- <sup>z</sup> Paper impregnated with a toluene solution of poly(methyl methacrylate), stearic acid, and 2-(p-tert-butylphenoxy)ethanol, then dried.
- aa Intramicellar impregnation of cellulose with the following swelling agents: n-propylamine, n-butylamine, n-hexylamine, 2-aminoethanol, dimethylformamide, acetic acid, dimethylsulfoxide, methylacetamide, dimethylacetamide, or formamide.
- bb Films cast from an approximately 4:3 mixture of a 20% solution and cellulose acetate butyrate in toluene-ethyl acetate (1:1) and triallycyanurate in dioxane.
- <sup>CC</sup> FILMS CAST FROM A 2:1 MIXTURE OF A 25% SOLUTION OF CELLULOSE ACETATE BUTYRATE IN TOLUENE-ETHYL ACETATE (1:1) AND THE TITANIUM ESTERS OF N,N,N', N'-TETRAKIS(2-HYDROXYPROPYL) ETHYLENEDIAMINE.
- <sup>dd</sup> Pure water.

- ee Films cast from aqueous gelatin or other hydrocolloids.
- ff Dimethylsulfoxide with methanolic KCN.
- gg 2-Methoxyethanol with methanolic KCN.
- hh Water or aqueous methanol containing bisulfite.
- ii Paper impregnated with m-dimethoxybenzene, acetonitrile, acetic acid, or phenyl methyl carbinol.
- jj Ethanol-benzene.
- <sup>kk</sup> Aqueous ethanol, methanol, aqueous methanol, aqueous acetone, benzene-methanol, carbon tetrachloride-methanol, cyclohexane-methanol, or chloroform-methanol.
- <sup>II</sup> Films cast from 3:1 solutions of cellulose acetate and either Polyethylene Glycol 600 .RTM. or ethylene glycol phenyl ether as plasticizer.
- mm Films, containing residual solvent, cast from solutions of either cellulose acetate in 2-methoxyethanol or poly(vinyl alcohol) in aqueous ethanol.
- <sup>nn</sup> Films, containing residual solvent, cast from solutions of either cellulose acetate butyrate in 2-methoxyethanol or poly(vinyl acetate) in methanol.
  - oo Ethanol containing ammonia.
  - pp Aqueous methanol containing NH<sub>4</sub> HSO<sub>3</sub> and urease.
  - <sup>qq</sup> Aqueous methanol containing NH<sub>4</sub> HSO<sub>3</sub>, with or without sodium dithionite.
  - " Aqueous acid at pH 1.
  - ss Aqueous ammonia containing KCN.
  - " Paper impregnated with aqueous solutions with or without hydrocolloids.
  - <sup>uu</sup> 2-Methoxyethanol containing HCl.
  - vv Aqueous methanol containing NH<sub>4</sub> HSO<sub>3</sub>, and glucose oxidase.
  - ww 9:1 Methanol-water.
  - xx Aqueous NaOH.]]

$$(CH_{3})_{2} = \begin{pmatrix} N(CH_{3})_{2} \\ X & C = O \\ 168 & X = (CH_{2})_{1,2} \end{pmatrix} = \begin{pmatrix} N(CH_{3})_{2} \\ N(CH_{3})_{2} \\ N(CH_{3})_{2} \end{pmatrix} = \begin{pmatrix} N(CH_{3})_{2} \\ N(CH_{3})_{2} \\ N(CH_{3})_{2} \end{pmatrix} = \begin{pmatrix} N(C_{2}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \end{pmatrix} = \begin{pmatrix} N(C_{2}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \end{pmatrix} = \begin{pmatrix} N(C_{2}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \\ N(C_{3}H_{3})_{2} \end{pmatrix} = \begin{pmatrix} N(C_{3}H_{3})_{2} \\ N(C_{3}H_{3}$$

175

## Photochromic Polymethine Dyes

(CH<sub>3</sub>)<sub>2</sub>N 
$$\stackrel{\alpha}{\longrightarrow}$$
  $C^+$  (CH=CH)<sub>n</sub>-CH=C  $\stackrel{\square}{\longrightarrow}$  N(CH<sub>3</sub>)<sub>2</sub>

Ar	n	
C <sub>6</sub> H <sub>5</sub>	0, 1, 2	
$4-(CH_3)_2NC_6H_4$	0, 1, 2	
4-(CH <sub>3</sub> ) <sub>2</sub> CHC <sub>6</sub> H <sub>4</sub>	0, 1, 2, 3, 4	
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	0, 1, 2	
4-C <sub>4</sub> H <sub>9</sub> OC <sub>6</sub> H <sub>4</sub>	0, 1, 2	
3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1, 2	
$4-t-C_4H_9C_6H_4$	1, 2	
4-C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub>	1, 2	
$4-C_5H_{11}C_6H_4$	1, 2	
4-FC <sub>6</sub> H <sub>4</sub>	1	
4-Fsub <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	1	
2-(C <sub>6</sub> H <sub>5</sub> )2NC6H4	1	
3,4-H <sub>2</sub> N(OCH <sub>3</sub> )C <sub>6</sub> H <sub>3</sub>	1	
2-Naphthyl	1, 2	
4-ClC <sub>6</sub> H <sub>4</sub>	2	
2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2	
1-Naphthyl	2	

$$\alpha$$
,  $\alpha$ -bis(p-dimethylaminophenyl)polyenes (CH<sub>3</sub>)<sub>2</sub>N  $C^+$   $N$ (CH<sub>3</sub>)<sub>2</sub>

$$-CH=C$$
 $N(CH_3)_2$ 
 $CF_3$ 

$$-CH = CCH_3 - N(CH_3)_2$$

$$-CH = CH - N(CH_2CH_2Cl)_2$$

$$-CH = CH - CH = CH - N(CH_3)_2$$

$$-CH = CH - N = N - N(CH_3)_2$$

$$-CH = CH - N = N - N(C_9H_5)_2$$

## Miscellaneous polyenes

Serial No. 10/828,558 Page 23 of 125

Basic Violet 7

Basic Red 13

Basic Red 14 Basic Red 15 Basic Violet 15

$$(CH_3)_2N$$
 $C=CH-CH=CH-C$ 
 $CIO_4$ 
 $N=N$ 

$$H_2N$$
 $CH_3$ 
 $CH_3$ 
 $CH_3$ 
 $CH_4$ 
 $CH_3$ 
 $CIO_4$ 
 $CH_3$ 

$$(CH_3)_2 \stackrel{\downarrow}{N}$$

$$C \longrightarrow N = N$$

$$(CH_3)_2 \stackrel{\downarrow}{N}$$

$$(CH_3)_2 \stackrel{\downarrow}{N}$$

$$\begin{array}{c} \overset{\leftarrow}{\text{CH}_3)_2N} & \overset{\leftarrow}{\text{N(CH}_3)_2} \\ \\ \overset{\leftarrow}{\text{C=CH-CH=CH-C}} & \overset{\leftarrow}{\text{CIO}_4} \\ \\ \overset{\leftarrow}{\text{CH}_3O} & \text{NH}_2 & \text{NH}_2 \\ \end{array}$$

$$\begin{array}{c} \text{CICH}_2\text{CH}_2\text{)2N} \\ \\ \text{C=CH-CH=CH-CH=CH-C} \\ \\ \text{F} \end{array}$$

$$CH_3O$$
 $CH_3$ 
 $CH_3$ 
 $CH_3$ 
 $CH_3$ 
 $CH_3$ 
 $CIO_4$ 
 $CH_3$ 

$$CH_{3}O$$
 $CH=CH-CH$ 
 $CH_{3}O$ 
 $CH_{3}O$ 
 $CH_{3}O$ 
 $CH_{3}O$ 

$$C-CH=CH$$
 $N(CH_2CH_2CI)_2$ 
 $CIO_4$ 

$$C=CH-CH$$
 $C=CH-CH$ 
 $C=CH-CH$ 
 $CIO_4$ 
 $CIO_4$ 

$$(CH_3)_2N$$

$$C \longrightarrow CH = CH - C$$

$$(CH_3)_2N$$

$$N(CH_3)_2$$

$$N(CH_3)_2$$

$$(CH_3)_2N$$

$$C=CH-N=N$$

$$O=$$

$$O=$$

$$O=$$

$$C_2H_5-N$$

$$C_2H_5-N$$

$$C_2H_5-N$$

$$C_2H_5$$

$$C_3H_5$$

$$C_$$

$$H_2N$$
 $C$ 
 $CH_3$ 
 $NH_2$ 
 $CH_3$ 
 $N(CH_3)_2$ 
 $N(CH_3)_3$ 
 $N(CH_3)_3$ 

$$N(C_2H_5)CH_2$$
 $N(C_2H_5)CH_2$ 
 $NH_2$ 
 $NH_2$ 
 $NH_2$ 
 $NH_2$ 
 $NH_3$ 
 $NH_4$ 
 $NH_4$ 
 $NH_5$ 
 $NH$ 

## Salt-isomerism type phototropic dyes

Night Blue

$$CH_3 \longrightarrow NH \longrightarrow C \longrightarrow N(C_2H_5)_2$$

$$N(C_2H_5)_2$$

$$N(C_2H_5)_2$$

Victoria Blue R

$$\stackrel{\cdot}{\underset{H}{\bigvee}} N - \stackrel{\cdot}{\underset{C}{\bigvee}} C = \stackrel{\cdot}{\underset{N(CH_3)_2}{\bigvee}} N - \stackrel{\cdot}{\underset$$

Brilliant Milling Blue B Brilliant Blue F & R Ex. Eriocyanine A

Methyl Blue

Aniline Blue

Eriochrome Cyanine R

Methyl Violet 6B

$$CH_3$$

$$CH_2-N$$

$$CH_2-N$$

$$CH_3)_2$$

$$N(CH_3)_2$$

Iodine Green

$$\begin{array}{c} \text{CH}_3\\ \text{CH}_3\text{CI}, \text{N} \\ \text{CH}_3 \\ \text{CH}_3 \\ \end{array}$$

Aniline Blue

$$CH_3$$
 $NH_2$ 
 $NH$ 
 $NH$ 
 $NH$ 

#### Serial No. 10/828,558 Page 33 of 125

Wool Violet 5 BN

Wool Violet 4 EM

$$(C_2H_5)_2N=$$
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 

Light Green SF Yellowish

$$C_2H_5$$
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_2H_5$ 
 $C_3N_3$ 

Iodine Violet

$$\begin{array}{c|c} CH_3 & & & \\ H & & & \\ C_2H_5 & & & \\ \end{array}$$

Methyl Violet

$$CH_3 \longrightarrow C \longrightarrow N(CH_3)_2 \longrightarrow N(CH_3)_2$$

Crystal Violet

$$CH_3 \atop CH_3 \atop N - C = N(CH_3)_2 \atop N(CH_3)_2$$

Ethyl Violet

$$(C_2H_5)_2N$$
 $C$ 
 $N(C_2H_5)_2$ 
 $N(C_2H_5)_2$ 

Acid Green L Extra

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

Erioviridene B

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$$

Light Green SF

Victoria Green (Malachite Green)

$$C = N(CH_3)_2$$

$$N(CH_3)_2$$

Red-Violet 5R

$$SO_3Na$$
 $NH_2$ 
 $CH_3$ 
 $H_2N$ 
 $C_2H_3$ 

Brilliant Green "B"

$$C = \bigvee_{N(C_2H_5)_2}^{\bullet} N(C_2H_5)_2$$

$$N(C_2H_5)_2$$

Di-[4(N,N-diethylamine)phenyl]-[4-(N,N-diethylamine-2-methyl) phenyl] methyl carbonium

$$(C_2H_5)_2N$$
  $C$   $N(C_2H_5)_2$   $N(C_2H_5)_2$ 

Tri-[4(N,N-dipropylamino)phenyl] methyl carbonium

$$\begin{array}{c|c} C_{3}H_{7} \\ \\ C_{3}H_{7} \end{array} N \longrightarrow \begin{array}{c} C_{3}H_{7} \\ \\ C_{3}H_{7} \\ \\ C_{3}H_{7} \\ \\ C_{3}H_{7} \end{array}$$

Di-[4(N,N-diethylamino)phenyl]-[4(ethylamino)phenyl] methyl carbonium

$$\begin{array}{c|c} H \\ C_2H_5 \\ \end{array} \qquad \begin{array}{c|c} C_2H_5 \\ \end{array} \qquad$$

Di-[4(N,N-diethylamino)phenyl]-[4(N,N-diethylamino)naphthyl] methyl carbonium

Di-[4(N,N-dimethylamino)phenyl]-[4(hydroxy)phenyl] methyl carbonium

HO — 
$$C$$
 —  $N < CH_3$   $CH_3$   $CH_3$   $CH_3$   $CH_3$   $CH_3$ 

Tri-[4(N-propylamino)phenyl] methyl carbonium

Hectolene Blue DS-1398
Hectolene Blue DS-1823
Sevron Brilliant Red 4G
Di-[4(N,N-dimethylamino)phenyi] [4(hydroxy)phenyl]
methyl carbonium

HO — 
$$C$$
 —  $N < CH_3$   $CH_3$   $CH_3$   $CH_3$   $CH_3$   $CH_3$ 

Tri-[4(N-propylamino)phenyl] methyl carbonium

Hectolene Blue DS-1398
Hectolene Blue DS-1823
Sevron Brilliant Red 4G
Genacryl Red 6B
Genacryl Pink G
Sevron Brilliant - Red B
Sevron Brilliant - Red 3B
1,5-bis-[4(N,N-dimethylamino)phenyl]-1,5-bis-(phenyl)divinyl carbonium trifluoroacetate

# 1,1,3,3-tetrakis[4(N,N-dimethylamino)phenyl] vinyl carbonium perchlorate

1,5-bis-[4(N,N-dimethylamino)phenyl]-1,5-bis-(phenyl) divinyl carbonium p-toluenesulfonate

C=CH-CH=CH-C 
$$\stackrel{\bullet}{\bigcirc}$$
  $\stackrel{\bullet}{\bigcirc}$  CH<sub>3</sub>  $\stackrel{\bullet}{\bigcirc}$  SO<sub>3</sub>-

1,7-bis[4(N,N-dimethylamino)phenyl]-1,7-bis-(2,4-dichlorophenyl) trivinyl carbonium perchlorate

$$\begin{array}{c} CI \\ CI \\ CI \\ CC \\ CCH \\ CCH$$

Di-[4(N,N-dimethylamino)phenyl vinyl]-[2,4-diphenyl-6-methane thiopyran] methyl carbonium perchlorate

$$CH = CH - N(CH_3)_2$$

1,7-bis-[4(N,N-dimethylamino)phenyl]-1,7-bis-(4-chlorophenyl) trivinyl carbonium trifluoroacetate

$$\begin{array}{c|c} CI & & & \\ & & & \\ C=CH-CH=CH-CH=CH-C \\ & & & \\ (CH_3)_2N & & & \\ \end{array}$$

# 1,1,3-tris-[4-(N,N-dimethylamino)phenyl] divinyl carbonium perchlorate

$$(CH_3)_2N$$
 $C=CH-C$ 
 $N(CH_3)_2$ 
 $CH_3)_2N$ 

#### $1,1,7,7\text{-tetrakis-} \big[4\text{-}(N,N\text{-dimethylamino})\text{phenyl}\big]$

trivinyl carbonium perchlorate

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ &$$

#### 1,3-bis-[4-(N,N-dimethylamino)phenyl]-1,3-bis-(phenyl) vinyl carbonium perchlorate

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

#### 1,1,5,5-tetrakis-[4-(N,N-dimethylamino)phenyl]

divinyl carbonium perchlorate

$$(CH_3)_2N \xrightarrow{C} C=CH-CH=CH-C$$

$$(CH_3)_2N \xrightarrow{C} N(CH_3)_2$$

$$(CH_3)_2N \xrightarrow{C} N(CH_3)_2$$

$$CIO_4-$$

#### 1,5-bis-[4-(N,N-dimethylamino)phenyl] -1,5-bis-

1,7-bis-[4-(N,N-dimethylamino)phenyl]-1,7-bis-(phenyl) trivinyl carbonium trifluoroacetate

$$\begin{array}{c|c} C & & & \\ \hline \\ C & & \\ \hline \\ (CH_3)_2 N & & \\ \hline \end{array}$$

CF<sub>3</sub>COO-

CIO<sub>4</sub>—

1(1,3,3-trimethyl indoline)-2-[4-(N,N-dimethyl-amino)phenyl] ethylene carbonium perchlorate

$$\begin{bmatrix} CH_3 \\ CH_3 \\ CH-CH \end{bmatrix} \xrightarrow{C} N(CH_3)_2$$

$$CIO_4-$$

1(1,3,3-trimethyl indoline)-4-[4-(N,N-dimethyl-amino)phenyl] butylene carbonium perchlorate

$$\begin{bmatrix} CH_3 \\ CH_3 \\ -CH-CH-CH-CH \end{bmatrix} \xrightarrow{\downarrow} N(CH_3)_2$$

1,1,3,3-tetrakis-[4(N,N-diethylamino)phenyl] vinyl carbonium perchlorate

$$(C_{2}H_{5})_{2}N - \bigcirc C = CH - C$$

$$(C_{2}H_{5})_{2}N - \bigcirc N(C_{2}H_{5})_{2}$$

$$ClO_{4} - \bigcirc N(C_{2}H_{5})_{2}$$

1,1-bis-[4-(N,N-diethylamino)phenyl]-3,3-bis-[4-(N,N-dimethylamino)phenyl] vinyl carbonium perchlorate

$$(C_2H_5)_2N$$
  $C=CH-C$   $N(CH_3)_2$   $N(CH_3)_2$   $N(CH_3)_2$ 

CIO<sub>4</sub>—

# 1,1,5,5-tetrakis-[4-(N,N-diethylamino)phenyl] divinyl carbonium perchlorate

C1O4-

# 1,1-bis-[4-(N,N-dimethylamino)phenyl]-3-[4-(amino) phenyl]-3-methylvinyl carbonium perchlorate

$$(CH_3)_2N \longrightarrow C=CH-C$$

$$(CH_3)_2N \longrightarrow CH_3$$

$$CH_3$$

$$CH_3$$

Tris-[1,1-bis-[4(N,N-dimethylamino)phenyl] ethylene] methyl carbonium perchlorate

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

ClO<sub>4</sub>—

Tris-[1,1-bis-[4-(N,N-diethylamino)phenyl] ethylene] methyl carbonium perchlorate

$$(C_{2}H_{5})_{2}N \xrightarrow{C} C=CH-C=CH-C$$

$$(C_{2}H_{5})_{2}N \xrightarrow{C} N(C_{2}H_{5})_{2}$$

$$(C_{2}H_{5})_{2}N \xrightarrow{C} C=C$$

$$(C_{2}H_{5})_{2}N \xrightarrow{C} CIO_{4}-$$

## 1,1,5-tris-[4-(N,N-dimethylamino)phenyl] divinyl carbonium perchlorate

$$\begin{array}{c} (CH_{3})_{2}N - \\ \\ (CH_{3})_{2}N - \\ \\ (CH_{3})_{2}N - \\ \\ CIO_{4}- \end{array}$$

N[4-(N,N-dimethylamino) cinnamylidene] auramine

$$(CH_3)_2N$$

$$C=N-CH=CH-CH$$

$$(CH_3)_2N$$

$$CIO_4-$$

## 1,1-bis-[4-(N,N-dimethylamino)phenyl-3,4-bis-(phenyl)]-3,4-diazo butene carbonium

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#### 1,1,5,5-tetrakis-[4-(N,N-dimethylamino)phenyl]-

#### 2,3-diazo pentene carbonium

N-(N',N'-dimethylamino cinnamylidene)-N,N-diphenyl ammonium

#### Azo Polymethines

Dyes of the general structural type

÷

$$(CH_3)_2N - \bigvee_{C=NH} + O = CH - CH = CH - \bigvee_{N(CH_3)_2} N(CH_3)_2 - \bigvee_{C=NHCH = CH - C} \bigvee_{N(CH_3)_2} N(CH_3)_2 - \bigvee_{N(C$$

- 31. (Original) The method of synthesis of the compound of claim 10 wherein the C moiety is any molecule which exhibits bleaching behavior with the B moiety and has an increased therapeutic effect or therapeutic ratio as a consequence of its delivery as part of a prodrug.
- 32. (Original) The method of synthesis of the compound of claim 29 wherein the C moiety has a nucleophilic group that bonds to the B moiety.
- 33. (Original) The method of synthesis of the compound of claim 32 wherein the C moiety is derivatized to have a nucleophilic group that bonds to the B moiety.
- 34. (Original) The method of synthesis of the compound of claim 33 wherein the C moiety is

Serial No. 10/828,558 Page 43 of 125

derivatized by at least one of the nucleophilic groups comprising cinnamate, sulfite, phosphate, carboxylate, thiol, amide, alkoxide, or amine.

35. (Currently Amended) The method of synthesis of the compound of claim 10 wherein the C moiety is at least one of the group of

Captopril

CH<sub>3</sub> O | COOH

Prostaglandin E<sub>2</sub>

C=C-C-C-C-C-CH<sub>3</sub>
H H H<sub>2</sub> H<sub>2</sub> H<sub>2</sub>
C=C-C-C-C-C-C-CH<sub>3</sub>
H H H<sub>2</sub> H<sub>2</sub> H<sub>2</sub>
H H H<sub>2</sub> H<sub>2</sub> H<sub>2</sub>

2,3-dichloro- $\alpha$ -methylbenzylamine

CI CI CH-NH<sub>2</sub> CH-NH<sub>2</sub> CH<sub>3</sub>

3'-deoxy-S-adenosyl-Lhomocysteine

Sinefungin

H<sub>2</sub>N CHCH<sub>2</sub>CH<sub>2</sub>C O N H H H H H OH

3,5-diiodo-4-hydroxybenzoic acid

но

6,6'-dithiobis (9-B-D-ribofuranosylpurine)

γ-aminobutyric acid

H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>COOH

#### Serial No. 10/828,558 Page 45 of 125

Gabaculine

COOH NH<sub>2</sub>

N-(5'-phosphopyridoxy)-4-aminobutyric acid OH CH2OP OH CH2NHCH2CH2CH2COOH

4-amino-hex-5-enoic acid

CH<sub>2</sub>=CHCHCH<sub>2</sub>CH<sub>2</sub>COOH | NH<sub>2</sub>

Baclofen

Adenosine

NH2 N N HOH2C O H H H H

3-hydroxy-3-methylglutarate

OH | CH3CH2CCH2COOH | CH3

Campactin

But-3-ynoyl-CoA

Suramin

L-3-iodotyrosine

 $L\text{-}3\text{-}iodo\text{-}\alpha\text{-}methyltyrosine}$ 

Disodium cromoglycate

#### Serial No. 10/828,558 Page 47 of 125

Adenosine 3',5'-cyclic monophosphate

$$\begin{array}{c|cccc}
& & & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & & \\
N & & & & & \\
N & & & & \\
N & & & & & \\
N & & & & & \\
N & & &$$

D,L-B-(5-hydroxy-3indolyl)-α-hydrazinopropionic acid

 $\begin{array}{ll} D_{r}L_{r}\alpha\text{-hydrazino-}\alpha\text{-}\\ methyldopa \end{array}$ 

α-methyldopa

5-(3,4-dihydroxycinnamoyl)salicylic acid

N-(phosphonacetyl)-L-aspartate

P-glycolohydroxamate

5-(p-sulfamylphenylazosalicylic acid

HO 
$$N=N$$
  $SO_2NH_2$ 

Coformycin

Formycin B

Thioinosinate

Phosphonoformate

Phosphonoacetate

Ridavirin

Sotalol

Cimetidine

Fuscaric acid

2-mercaptoethylamine

HSCH<sub>2</sub>CH<sub>2</sub>NH<sub>3</sub>+

Mimosine

U-7130

Iproniazid

Trans-4-aminoocrotonic

acid

$$H_2NCH_2CH = CHCOOH$$

NSD 1055

Nicotinic acid

Kynurenic acid

Lentysine

Orotic acid

Polyoxin D

Cephalosporin

Penicillin

#### 36. (Canceled)

- 37. (Original) The method of synthesis of the compound of claim 1 wherein the C moiety comprises at least one of the group of herbicides, fungicides, miticides, nematocides, fumigants, growth regulators, repellants, defoliants, rodenticides, molluscicides, algicides, desicants, antehelmintics, and bactericides.
- 38. (Currently Amended) The method of synthesis of the compound of claim 37 wherein the C moiety is a pesticide one from the those given in Chemical Week Pesticides Register, Robert

Serial No. 10/828,558 Page 51 of 125

P. Ovellette and John A. King, 1977, McGraw-Hill Book Company.

39. (Withdrawn) A method of synthesis of a chemical compound having the formula  $(A-B-C)_X-P-E_Y$ 

where the A is a chemiluminescent moiety,

B is an energy acceptor moiety, and

C is a biologically active moiety, and

P is a substrate

E is an enzyme and x and y are integers

comprising the steps of

forming a benzophenone,

forming a diaryl ethylene,

attaching a phthalimide moiety to at least one of the aryl groups of the ethylene to form a phthalimide-ethylene conjugate,

condensing two ethylene-phthalimide conjugates to form a phthalimide-pentadiene conjugate,

converting the phthalimide to the phthalhydrazide by reaction with hydrazine to form a carrier compound, and

reacting the carrier compound with a biologically active moiety to form a corresponding conjugate,

reacting A-B-C with a polymer to form  $(A-B-C)_X-P$ , and reacting E with  $(A-B-C)_X-P$  to form  $(A-B-C)_X-P-E_Y$ .

- 40. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the compound provides controlled extra cellular release of the C moiety.
- 41. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the C moiety comprises at least one of drugs and proteins including enzymes and hormones.
- 42. (Withdrawn) The method of synthesis of the compound of claim 41 wherein the C moiety comprises at least one insulin, erythropoietin, interleuken 2, interferon, growth hormone, atrial natriuretic factor, tissue plasminogen activator, an anti-inflammatory drug, an antihypertensive drug, an inotropic drug, and a contraceptive drug.

- 43. (Withdrawn) The method of synthesis of the compound of claim 40 wherein extraacellular drug release occurs when the prodrug reacts with cellular free radicals via a mechanism involving chemiluminescence, photochromism, and intramolecular energy transfer.
- 44. (Withdrawn) The method of synthesis of the compound of claim 41 wherein the pharmaceutical agent is at least one of the group of antilipidemic drugs, anticholesterol drugs, contraceptive agents, anticoagulants, anti-inflamatory agents, immuno-suppressive drugs, antiarrhythmic agents, antineoplastic drugs, antihypertensive drugs, epinephrine blocking agents, cardiac inotropic drugs, antidepressant drugs, diuretics, antifungal agents, antibacterial drugs, anxiolytic agents, sedatives, muscle relaxants, anticonvulsants, agents for the treatment of ulcer disease, agents for the treatment of asthma and hypersensitivity reactions, antithroboembolic agents, agents for the treatment of muscular dystrophy, agents to effect a therapeutic abortion, agents for the treatment of anemia, agents to improve allograft survival, agents for the treatment of disorders of purine metabolism, agents for the treatment of ischemic heart disease, agents for the treatment of opiate withdrawal, agents which activate the effects of secondary messenger inositol triphosphate, agents to block spinal reflexes, and antiviral agents including a drug for the treatment of AIDS.
- 45. (Withdrawn) The method of synthesis of the compound of claim 43 wherein the C moiety is released by an oxidation reduction reaction with the target cell's electron carriers or by reaction with free radicals produced as a consequence of electron transport.
- 46. (Withdrawn) The method of synthesis of the compound of claim 43 wherein A represents a functionality which undergoes at least one of

an oxidation reduction reaction where electrons are transferred directly between A and the target cell's electron carriers, and

a reaction with free radicals of oxygen which are produced as a consequence of electron transport

such that an excited state is produced in A as a consequence of its participation in one of these reactions.

47. (Withdrawn) The method of synthesis of the compound of claim 46 wherein A undergoes intramolecular energy transfer from its own excited state to the B functionality which is an energy acceptor.

- 48. (Withdrawn) The method of synthesis of the compound of claim 47 wherein upon receiving energy from A, B achieves an excited state which relaxes through heterolytic cleavage of the covalent bond of B with C where C is a drug moiety which is released into the environment.
- 49. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the chemiluminescent molecule comprises at least one of the group of

molecules undergoing reaction involving peroxides and oxygen free radicals, molecules undergoing reaction involving oxidation or reduction, and molecules undergoing both reaction with peroxides and oxygen free radicals followed by an oxidation or reduction reaction.

- 50. (Withdrawn) The method of synthesis of the compound of claim 49 wherein the chemiluminescent molecule comprises at least one of the group of luminol and its derivatives, lucigenin and its derivatives, Lophine and its derivatives, acridinium esters and acridans, tetraphenylpyrrole, phthalhydrazides, acyloins, biacridinium salts, vinylcarbonyls, vinylnitriles, tetrakis (dimethylamino) ethylene, acyloperoxides, indoles, tetracarbazoles and active oxalates.
- 51. (Withdrawn) The method of synthesis of the compound of claim 49 wherein the chemiluminescent molecule comprises at least one of the group of ruthenium chelates 2, 6-diaminopyrene, or cation radicals and molecules which follow a Chemically Initiated Electron Exchange Luminescence mechanism such as certain dioxetans and dioxetanones.
- 52. (Withdrawn) The method of synthesis of the compound of claim 49 wherein the chemiluminescent molecule comprises at least one of the group of dioxene derivatives and other compounds that form a dioxetan by reaction with superoxide and then produce efficient chemiluminescence by a CIEEL mechanism.
- 53. (Withdrawn) The method of synthesis of the compound of claim 49 wherein the chemiluminescent molecule comprises at least one of the group of

#### Serial No. 10/828,558 Page 54 of 125

2,6-diaminopyrene

Aminophthalhydrazide

#### TABLE 1

### Representative Chemiluminescent Molecules

Name

Structure

#### Serial No. 10/828,558 Page 55 of 125

Dioxene

$$O$$
 $R_1$ 
 $R_2$ 

Imidazole derivatives

$$R_1 \stackrel{N}{\longleftarrow} R_2$$

$$R_1 \stackrel{N}{\longleftarrow} R$$

Sulfonyloxamides

Indole derivatives

Tetrakis(dialkylamino)ethylene

2,5,7,8-tetraoxabicyclo-[4.2.0.] octane

Dioxetan

$$R_1$$
 $R_2$ 
 $R_2$ 
 $R_3$ 

Lucigenin

#### TABLE 1 continued

### Representative Chemiluminescent Molecules

Name	Structure
Lophine .	
	N N
Acridinium esters	CH3 X-N+ X-
Active oxalate	
Tris-2,2'-bipyridinedi- chlororuthenium (II)	(\(\bigc\)_N =\(\bigc\))3
Dioxetanone	CI $CI$ $CI$ $CI$
Dipheyl peroxide	$O$ $R_1$ $R_2$
Diplieyi peroxiae	

- 54. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the B moiety is a photochromic compound.
- 55. (Withdrawn) The method of synthesis of the compound of claim 54 wherein the photochromic compound comprises one which demonstrate photochromic behavior with electromagnetic radiation and bleaching agents.
- 56. (Withdrawn) The method of synthesis of the compound of claim 55 wherein the A functionality is chemiluminescent, and the B functionality is such that the photodissociative drug release spectrum of B overlaps the chemiluminescence spectrum of A.
- 57. (Withdrawn) The method of synthesis of the compound of claim 54 wherein the photochromic compound comprises a cationic dye.
- 58. (Withdrawn) The method of synthesis of the compound of claim 57 wherein the cationic dye comprises at least one of a di and triarylmethane dyes, triarylmethane lactones and cyclic ether dyes, cationic indoles, pyronines, phthaleins, oxazines, thiazines, acridines, phenazines, and anthocyanidins, and cationic polymethine dyes and azo and diazopolymethines, styryls, cyanines, hemicyanines, dialkylaminopolyenes, and other related dyes.
- 59. (Withdrawn) The method of synthesis of the compound of claim 57 wherein the cationic dye comprises at least one of

2,6-diaminopyrene 
$$\begin{array}{c} NH_2 \\ NH_2 \\ NH_2 \\ NH_2 \\ NH_3 \\ NH_4 \\ NH_5 \\ NH_6 \\ NH_8 \\ NH_8$$

Dioxene

$$O$$
 $O$ 
 $R_1$ 
 $R_2$ 

Imidazole derivatives

$$R_1 \stackrel{N}{\longleftarrow} R_2$$

$$R_1 \stackrel{N}{\longleftarrow} R$$

Sulfonyloxamides

Indole derivatives

Tetrakis (dialkylamino)ethylene

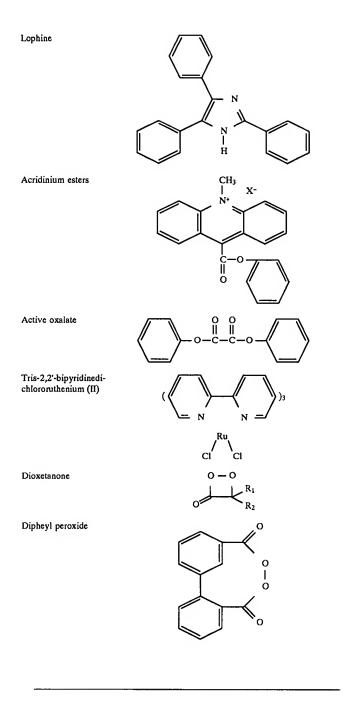
2,5,7,8-tetraoxabicyclo-[4.2.0.] octane

$$\begin{array}{c|c}
 & O & O \\
 & R_2 & R_1 \\
 & O - O & R_2
\end{array}$$

Dioxetan

$$0-0$$
 $R_2$ 
 $R_3$ 
 $R_4$ 

Lucigenin



60. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the C moiety is any molecule which exhibits bleaching behavior with the B moiety and has an increased therapeutic effect or therapeutic ratio as a consequence of its delivery as part of a prodrug.

Serial No. 10/828,558 Page 60 of 125

- 61. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the C moiety has a nucleophilic group that bonds to the B moiety.
- 62. (Withdrawn) The method of synthesis of the compound of claim 61 wherein the C moiety is derivatized to have a nucleophilic group that bonds to the B moiety.
- 63. (Withdrawn) The method of synthesis of the compound of claim 62 wherein the C moiety is derivatized by at least one of the nucleophilic groups comprising cinnamate, sulfite, phosphate, carboxylate, thiol, amide, alkoxide, or amine.
- 64. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the C moiety is at least one of the group of

Captopril

Prostaglandin E<sub>2</sub>

2,3-dichloro- $\alpha$ -methylbenzylamine

3'-deoxy-S-adenosyl-L-homocysteine

Sinefungin

3,5-diiodo-4-hydroxybenzoic acid

6,6'-dithiobis (9-B-D-ribofuranosylpurine)

γ-aminobutyric acid

H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>COOH

#### Serial No. 10/828,558 Page 62 of 125

Gabaculine

N-(5'-phosphopyridoxy)-4-aminobutyric acid

4-amino-hex-5-enoic acid

Baclofen

Adenosine

3-hydroxy-3-methylglutarate

Campactin

$$\begin{array}{c} \text{CH}_2 = \text{CHCHCH}_2\text{CH}_2\text{COOH} \\ \downarrow \\ \text{NH}_2 \end{array}$$

But-3-ynoyl-CoA

Suramin

$$SO_{3}^{-} \longrightarrow NH - C$$

$$SO_{3}^{-} \longrightarrow NH - C$$

$$NH \longrightarrow C \longrightarrow NH$$

$$C = O$$

$$C$$

L-3-iodotyrosine

 $L\text{-}3\text{-}iodo\text{-}\alpha\text{-}methyl tyrosine}$ 

Disodium cromoglycate

Adenosine 3',5'-cyclic monophosphate

D,L-B-(5-hydroxy-3indolyl)-α-hydrazinopropionic acid

D,L-α-hydrazino-αmethyldopa

α-methyldopa

5-(3,4-dihydroxycinnamoyl)salicylic acid

N-(phosphonacetyl)-L-aspartate

P-glycolohydroxamate

5-(p-sulfamylphenylazosalicylic acid

HO 
$$N=N$$
  $SO_2NH_2$ 

Coformycin

Formycin B

Thioinosinate

Phosphonoformate

Phosphonoacetate

Ridavirin

$$\begin{array}{c|c} H_2NC & N & O^- \\ \parallel & & & \\ O & & & \\ N & O & CH_2-P-O \\ \parallel & & \\ N & OH & OH \end{array}$$

Sotalol

$$\begin{array}{c} O \\ \parallel \\ CH_3SNH \\ \parallel \\ O \end{array} \begin{array}{c} OH \\ \uparrow \\ CHCH_2NHCH(CH_3)_2 \\ \parallel \\ O \end{array}$$

Cimetidine

$$\stackrel{CH_3}{\searrow} \stackrel{CH_2SCH_2CH_2N=C}{\stackrel{NHCH_3}{\searrow}} \\ NHC \equiv N$$

Fuscaric acid

2-mercaptoethylamine

 $\mathrm{HSCH_2CH_2NH_3}^+$ 

Mimosine

U-7130

Iproniazid

Trans-4-aminoocrotonic

acid

NSD 1055

Nicotinic acid

Kynurenic acid

Lentysine

Orotic acid

Polyoxin D

Cephalosporin

R<sub>1</sub>NH S R<sub>2</sub>

Penicillin

RCNH S CH<sub>2</sub>

- 65. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the A-B-C moieties are attached to P by a bond between P and at least one of A and B.
- 66. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the E moieties are attached to  $(A-B-C)_X-P$  by a bond between E and at least one of A, B, and P.
- 67. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the E moieties are enzymes that react with a desired substrate and form substances that cause the

Serial No. 10/828,558 Page 68 of 125

release of C from A-B-C.

- 68. (Withdrawn) The method of synthesis of the compound of claim 39 wherein the E moieties are enzymes that react with a desired substrate and form peroxide or free radicals that cause the release of C from A-B-C.
- 69. (Withdrawn) The method of synthesis of the compound of claim 67 wherein the E moiety, substrate, and C moiety are at least one of the group of

glucose oxidase, glucose, and insulin, and xanthine oxidase, xanthine, and tissue plasminogen activator (TPA).

70. (Withdrawn)A method of synthesis of a chemical compound having the formula (A-B-C)<sub>X</sub>-P

where the A is a chemiluminescent moiety,

B is an energy acceptor moiety, and

C is a biologically active moiety, and

P is a substrate and x is an integer

comprising the steps of

forming a benzophenone,

forming a diaryl ethylene,

attaching a phthalimide moiety to at least one of the aryl groups of the ethylene to form a phthalimide-ethylene conjugate,

condensing two ethylene-phthalimide conjugates to form a phthalimide-pentadiene conjugate,

converting the phthalimide to the phthalhydrazide by reaction with hydrazine to form a carrier compound, and

reacting the carrier compound with a strong base such as an alkali hydride and the biologically active moiety to form a corresponding conjugate,

reacting A-B-C with a polymer to form (A-B-C)<sub>X</sub>-P.

- 71. (Original) The method of synthesis of the compound of claim 1 wherein one or more of the moieties can be modified to further candidate components by addition of functional groups.
- 72. (Currently Amended) The method of synthesis of the compound of claim 71 wherein the groups comprise at least on one of alkyl, cycloalkyl, alkoxycarbonyl, cyano, carbamoyl,

heterocyclic rings containing C, O, N, S, sulfo, sulfamoyl, alkoxysulfonyl, phosphono, hydroxyl, halogen, alkoxy, alkylthiol, acyloxy, aryl, alkenyl, aliphatic, acyl, carboxyl, amino, cyanoalkoxy, diazonium, carboxyalkylcarboxamido, alkenylthio, cyanoalkoxycarbonyl, carbamoylalkoxycarbonyl, alkoxy carbonylamino, cyanoalkylamino, alkoxycarbonylalkylamino, sulfoalkylamino, alkylsulfamoylaklylamino, oxido, hydroxy alkyl, carboxy alkylcarbonyloxy, cyanoalkyl, carboxyalkylthio, arylamino, heteroarylamino, alkoxycarbonyl, alkylcarbonyloxy, cyanoalkoxy, alkoxycarbonylalkoxy, carbamoylalkoxy, carbamoylalkyl carbonyloxy, sulfoalkoxy, nitro, alkoxyaryl, halogenaryl, amino aryl, alkylaminoaryl, tolyl, alkenylaryl, alkenyloxyaryl. allylaryl, allyloxyaryl, cyanoaryl, carbamoylaryl, carboxyaryl, alkoxycarbonylaryl, alkylcarbonyoxyaryl, sulfoaryl, alkoxysulfoaryl, sulfamoylaryl, and nitroaryl.

73. (Currently Amended) The method of synthesis of the compound of claim1 wherein the compound has the structure of general formula

where R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are functional groups and L is a linker.

74. (Original) The method of synthesis of the compound of claim 73 wherein the functionality A is at least one of aminophthalhydrazide derivatives, sulfonyloxamides and active oxalates,

the functionality B is at least one of 1,1,5,5-tetrakisarylpentadiene and 1,1,5-trisarylpentadiene derivatives,

the functionality C is a drug molecule such as Foscarnate, or ddc;, and

R is a functional group, and

L is a linker such as an aliphatic chain between A and B.

75. (Original) The method of synthesis of the compound of claim 74 wherein the L functionality is between one 20 carbon atoms.

76. (Currently Amended) The method of synthesis of the compound of claim 1 wherein B is a 1,1,5-trisarylpentadiene derivative and the compound has the formula

where R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are functional groups and L is a linker.

77. (Currently Amended) The method of synthesis of the compound of claim 1 wherein A is a sulfonyloxamide or active oxalate and the compound has the formula

where R<sup>1</sup> and R<sup>2</sup> are functional groups and L is a linker.

- 78. (Original) The method of synthesis of the compound of claim 1 wherein a luminol derivative is directly attached through one or more amino groups to the aryl groups of a photochromic dye.
- 79. (Currently Amended) The method of synthesis of the compound of claim 78 wherein C comprises the formula of at least one of

Serial No. 10/828,558 Page 71 of 125

ddc , and A-B comprises the formula of at least one of

YY99811-1

Serial No. 10/828,558 Page 72 of 125

6a

GZW2-33-1 C<sub>37</sub>H<sub>38</sub>N<sub>5</sub>O<sub>2</sub> • ClO<sub>4</sub> M.W. 684.20 Serial No. 10/828,558 Page 73 of 125

G2W1-98-2 C<sub>49</sub>H<sub>41</sub>N<sub>6</sub>O<sub>4</sub> • BF<sub>4</sub> M.W. 864.71

, and

### MTLJ-1

$$\begin{array}{c} & & & & \\ & & & \\ & & & \\ & &$$

80. (Currently Amended) The method of synthesis of the compound of claim 78 wherein the compound comprises the formula

## MTLJ-1-Foscarnet

$$(CH_2)_4NH(CH_2)_2 \qquad (CH_2)_2NH(CH_2)_4 \qquad NH$$

- 81. (Original) The method of synthesis of the compound of claim 1 wherein the hydrolyzable group that protects phthalhydrazide is at least one of acetyl and t-butyloxycarbonyl.
- 82. (Original) The method of synthesis of the compound of claim 1 wherein the aminophthalimide-substituted precursors for the dye are prepared through amination of an aryl halide such as palladium-catalyzed amination of aryl halides.
- 83. (Original) The method of synthesis of the compound of claim 1 wherein halo-substituted aryl groups of a starting B moiety or an intermediate are coupled with the aminophthalimide by methods such as the aryl amination under palladium catalysis to form the aminophthalimide-substituted precursors for the dye.
- 84. (Original) The method of synthesis of the compound of claim 1 wherein halo-substituted aryl groups of a starting phthalimide or an intermediate are coupled with the amino-substituted dye by methods such as the aryl amination under palladium catalysis to form the aminophthalimide-substituted precursors for the dye.
- 85. (Currently Amended) The method of synthesis of the compound of claims 83-and 84 wherein amino-substituted aryl groups are obtained by the amination of the halo-substituted compounds with an imine such as benzophenoneimine.
- 86. (Original) The method of synthesis of the compound of claim 1 wherein the

aminophthalimide-attached dye is formed by the condensation of two aminophthalimide-attached ethylene molecules by reaction with triethyl orthoformate and a strong acid such as perchloric acid in acetic anhydride or acetic acid.

- 87. (Original) The method of synthesis of the compound of claim 1 wherein during the step of converting the phthalimide moiety to the aminophthalhydrazide to obtain A-B, the B moiety is protected from reaction with hydrazine by reacting with base such as sodium hydroxide, sodium methoxide and amines.
- 88. (Original) The method of synthesis of the compound of claim 87 wherein the phthalimide-B conjugate with a protected B moiety is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent in inert atmosphere and then treated with acid such as perchloric acid, tetrafluroboric acid to regenerate a corresponding unaltered B moiety of the A-B conjugate.
- 89. (Original) The method of synthesis of the compound of claim 88 wherein A-B is reacted with one nucleophilic species of C to form A-B-C.
- 90. (Original) The method of synthesis of the compound of claim 1 wherein A-B is formed by starting with B comprising halo-substituted dyes, such as 1,5-bis(p-bromophenyl)-1,5-bis(p-dimethylaminophenyl)-pentadienium perchlorate.
- 91. (Original) The method of synthesis of the compound of claim 90 wherein cationic dyes are protected by reacting with base such as alkoxide and then coupled with the aminophthalimide by amination of aryl halide such as the palladium-catalyzed amination of aryl halide to obtain the alkoxide-protecting aminophthalimide-substituted dyes.
- 92. (Original) The method of synthesis of the compound of claim 91 wherein the aminophthalimide-B conjugate with a protected B moiety is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent to convert the amino-phthalimide moiety to the aminophthalhydrazide moiety and then treated with acid to generate A-B.
- 93. (Original) The method of synthesis of the compound of claim 1 wherein the B comprises a tetraarylpolymethine, the aminophthalhydrazide precursor is an aminophthalic acid diester and the conjugate to form A-B is amino-phthalimideluminol-tetraaryl-polymethine.

94. (Currently Amended) The method of synthesis of the compound of claim 1 wherein halosubstituted diarylketone are formed by at least one of direct acylation of arene with halosubstituted benzoyl halide under ferric chloride catalysis according to the following representative scheme

acylation according to the following representative scheme

Br Cl 1) aniline, Na<sub>2</sub>CO<sub>3</sub>

2) 
$$N,N$$
-dimethylaniline, POCl<sub>3</sub>

1a: R = N(CH<sub>3</sub>)<sub>3</sub>

- 95. (Original) The method of synthesis of the compound of claim 1 wherein a halo-substituted diarylketone is converted to the corresponding halo-substituted diarylketene such as halo-substituted 1,1-diarylethene.
- 96. (Original) The method of synthesis of the compound of claim 95 wherein the halo-substituted diarylketene is coupled with a precursor of amino-phthalhydrazide such as aminophthalimide, aminophthalic acid diester, by aryl amination such as the palladium-catalyzed amination of aryl halides to form the aminophthalimide-substituted 1,1-diarylethene.
- 97. (Original) The method of synthesis of the compound of claim 96 wherein the ethene is condensed with an orthoester such as triethylorthoformate in a nonaqueous solvent such as acetic anhalydide, containing an acid catalyst such as perchloric acid, tetrafluoroboric acid, to form the aminophthalimide-substituted tetraarylpolymethine dye.
- 98. (Original) The method of synthesis of the compound of claim 97 wherein the aminophthalimide moiety is converted to the aminophthalhydrazide to obtain A-B.

- 99. (Original) The method of synthesis of the compound of claim 98 wherein the B moiety is a cationic dye that is first protected by reacting with an anion such as hydroxide, methoxide and amine and the phthalimide-B conjugate with a protected B moiety is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent in inert atmosphere and then treated with acid such as perchloric acid, tetrafluroboric acid to regenerate a corresponding unaltered B moiety of the A-B conjugate.
- 100. (Original) The method of synthesis of the compound of claim 99 wherein A-B is reacted with one nucleophilic species of a C such as a drug 2',3'-dideoxycytidine, Foscarnet, acycloguanosine to form A-B-C comprising a prodrug.
- 101. (Original) The method of synthesis of the compound of claim 95 wherein two halo-substituted diarylketene precursor compounds are condensed with an orthoester such as triethylorthoformate in a nonaqueous solvent such as acetic anhydride containing acid catalyst such as perchloric acid, tetrafluoroboric acid to form the halo-substituted tetraarylpolymethine dyes such as 1,5-bis(p-bromophenyl)-1,5-bis(p-dimethylaminophenyl)-pentadienium perchlorate.
- 102. (Original) The method of synthesis of the compound of claim 101 wherein the B moiety is a cationic dye that is protected by reacting with an anion such as alkoxide and then coupled with the aminophthalimide by amination of aryl halide such as the palladium-catalyzed amination of aryl halide to obtain the alkoxide-protected aminophthalimide-substituted tetraarylpolymethine dye.
- 103. (Original) The method of synthesis of the compound of claim 103 wherein the alkoxide-protected aminophthalimide-substituted tetraarylpolymethine dye is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent to convert the amino-phthalimide moiety to the aminophthalhydrazide moiety and then treated with acid to generate A-B comprising a luminol-tetraarylpolymethine compound.
- 104. (Currently Amended) The method of synthesis of the compound of claim 1 comprising the general steps given by following representative formula

Serial No. 10/828,558 Page 78 of 125

1) aniline, Na<sub>2</sub>CO<sub>3</sub>

2) N,N-dimethylaniline, POCl<sub>3</sub>

1a:  $R = N(CH_3)_3$ 

1c: R = OCH<sub>3</sub>

**1d**: R =  $O(CH_2)_3CH_3$ 

1e:  $R = (CH_2)_3CH_3$ 

CH<sub>3</sub>MgBr

FeCl<sub>3</sub>

1a:  $R = N(CH_3)_2$ 

1b: R = H

1c: R = OCH<sub>3</sub>

**1d**:  $R = O(CH_2)_3CH_3$ 

1e:  $R = (CH_2)_3CH_3$ 

**2a**:  $R = N(CH_3)_2$ 

2b: R = H

**2c**: R = OCH<sub>3</sub>

**2d**:  $R = O(CH_2)_3CH_3$ 

**2e**:  $R = (CH_2)_3CH_3$ 

 $Pd(OAc)_2$ ,  $P(t-Bu)_3$ ,

t-BuONa

3a:  $R = N(CH_3)_2$ 

**3b**: R = H

3c: R = OCH<sub>3</sub>

**3d**:  $R = O(CH_2)_3CH_3$ 

**3e**:  $R = (CH_2)_3CH_3$ 

$$(H_3C)_2N$$
 $H_NC)_2N$ 
 $H_N$ 

3-(N-Ethylamino)-N,6-dimethylphthalimide

4f

Serial No. 10/828,558 Page 80 of 125

**3a**:  $R = N(CH_3)_2$ 

3b: R = H

3c: R = OCH<sub>3</sub>

**3d**:  $R = O(CH_2)_3CH_3$ 

**3e**:  $R = (CH_2)_3CH_3$ 

$$\begin{array}{c} R \\ C - C = C \\ H \end{array}$$

1) KOH, 2) H<sub>2</sub>NNH<sub>2</sub>, 3) HX

4a:  $R = N(CH_3)_2$ ,  $X = CIO_4$ 

4b: R = H, X = BF<sub>4</sub>

**4c**:  $R = OCH_{3}$ ,  $X = BF_{4}$ 

**4d**:  $R = O(CH_2)_3CH_3$ ,  $X = BF_4$ 

**4e**:  $R = (CH_2)_3CH_3$ ,  $X = BF_4$ 

**5b**: R = H, X = BF<sub>4</sub>

**5c**:  $R = OCH_3$ ,  $X = BF_4$ 

**5d**:  $R = O(CH_2)_3CH_3$ ,  $X = BF_4$ 

**5e**:  $R = (CH_2)_3CH_3$ ,  $X = BF_4$ 

105. (Original) The method of synthesis of the compound of claim 1 wherein the A

Serial No. 10/828,558 Page 82 of 125

functionality comprises a phthalhydrazide such as a luminol derivative and the B functionality comprises a photochromic dye wherein A is attached to aryl groups of B comprising the steps of

forming a diaryl ketone,

forming a diaryl ketene from the diaryl ketone,

forming a protected aminophthalhydrazide such as aminophthalimide or aminophthalic acid diester,

adding a hydrocarbon linker to the protected aminophthalhydrazide, and

attaching the protected aminophthalhydrazide through the molecular linker to the aryl groups of diarylketene to form the precursor aminophthalimide-linked diarylketene, and reacting according to at least one of

- (a) forming the A functionality from the precursor, and condensing two molecules of B precursor linked to A to form A-B, and
- (b) condensing two precursor aminophthalimide-linked diarylketene molecules to form A precursor linked to B, and

forming the A functionality from the A precursor to form A-B.

- 106. (Original) The method of synthesis of the compound of claim 105 wherein the diaryl ketone is formed by a classical Friedel-Crafts acylation between a benzoyl halide and aryl compound with a hydrocarbon linker having a leaving group.
- 107. (Original) The method of synthesis of the compound of claim 106 wherein the aryl compound with a hydrocarbon linker having a leaving group comprises at least one of a halogenated-alkyl-aryl ether and a halogenated-alkyl-aryl amine wherein the halogen is the leaving group.
- 108. (Original) The method of synthesis of the compound of claim 107 wherein the halogenated-alkyl-aryl ether comprises 2-bromoethoxybenzene to give an aryl ketone such as 4-(2-bromoethoxy)benzophenone.
- 109. (Original) The method of synthesis of the compound of claim 107 wherein the halogenated-aklyl-aryl amine comprises 2-bromoethyl aminobenzene to give an aryl ketone such as 4-(2-bromoethyl amino)benzophenone.
- 110. (Original) The method of synthesis of the compound of claim 105 wherein the diaryl ketone is converted to the corresponding diarylketene by reacting with a methylating reagent such

as a methyl Grignard reagent, methyl lithium reagent, lithium dimethylcopper reagent and then dehydration with acid.

- 111. (Original) The method of synthesis of the compound of claim 110 wherein the diaryl ketone is converted to the corresponding diarylketene by reacting with methylmagnesium bromide and then dehydration with acid.
- 112. (Original) The method of synthesis of the compound of claim 105 wherein the diaryl ketone is converted to the corresponding diarylketene by a Wittig reaction.
- 113. (Original) The method of synthesis of the compound of claim 105 wherein a linker is attached to the protected aminophthalhydrazide by a reaction of a nucleophilic group of the linker or protected aminophthalhydrazide with a leaving group of the linker or protected aminophthalhydrazide.
- 114. (Original) The method of synthesis of the compound of claim 105 wherein a linker is attached to the protected aminophthalhydrazide by reaction to form a bond between at least one of a nitrogen, oxygen, or carbon atom of the linker and at least one of a nitrogen, oxygen, or carbon atom of group of the protected aminophthalhydrazide by an addition or a substitution reaction of a leaving group.
- 115. (Original) The method of synthesis of the compound of claim 114 wherein a linker is attached to the protected aminophthalhydrazide by a substitution reaction of at least one of a halogen, tosylate group, ester group with a nitrogen, oxygen, or carbon atom.
- 116. (Original) The method of synthesis of the compound of claim 105 wherein attaching the protected aminophthalhydrazide through the molecular linker to one of the aryl groups of diarylketene to form the precursor aminophthalimide-linked diarylketene is by a reaction of a nucleophilic group of the linker or aryl group of diarylketene with a leaving group of the linker or aryl group of diarylketene.
- 117. (Original) The method of synthesis of the compound of claim 116 wherein a linker is attached to the aryl group of diarylketene by reaction to form a bond between at least one of a nitrogen, oxygen, or carbon atom of the linker and at least one of a nitrogen, oxygen, or carbon atom of group of the protected aminophthalhydrazide by an addition or a substitution reaction of

a leaving group.

- 118. (Original) The method of synthesis of the compound of claim 117 wherein a linker is attached to the aryl group of diarylketene by a substitution reaction of at least one of a halogen, tosylate group, ester group with a nitrogen, oxygen, or carbon atom.
- 119. (Original) The method of synthesis of the compound of claim 105 wherein the precursor aminophthalimide-linked diarylketene is further reacted by condensation aminophthalimide-linked diarylketenes with an orthoester to form B linked to the A precursor.
- 120. (Original) The method of synthesis of the compound of claim 119 wherein condensing reagent is triethylorthoformate.
- 121. (Currently Amended) The method of synthesis of the compound of claim 119 wherein the precursor aminophthalimide-linked diarylketene comprises at least one of the formula

12d:  $R=N(CH_3)_2$ 

and the precursor of A-B comprises at least one of the formula

19a: R=OCH<sub>3</sub> 19b: R=O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> **19c:**  $R = (CH_2)_3 CH_3$ **19d:**  $R=N(CH_3)_2$ 

122. (Original) The method of synthesis of the compound of claim 119 wherein the phthalimide moiety of the A precursor is converted to the phthalhydrazide A functionality by treating with hydrazine, forming A-B.

- 123. (Original) The method of synthesis of the compound of claims 122 wherein the B functionality is protected by reacting with an anion such as hydroxide, methoxide and amine, the A-B precursor is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent in inert atmosphere and then treated with acid such as perchloric acid, tetrafluroboric acid to form A-B.
- 124. (Original) The method of synthesis of the compound of claim 105 wherein the phthalimide moiety of the A precursor of the precursor aminophthalimide-linked diarylketene is converted to the phthalhydrazide A functionality by treating with hydrazine, forming A attached to a B precursor.
- 125. (Original) The method of synthesis of the compound of claim 124 wherein the A-linked diarylketene is further reacted by condensation of two A-linked diarylketenes with an orthoester to form A-B.
- 126. (Original) The method of synthesis of the compound of claim 125 wherein condensing reagent is triethylorthoformate.
- 127. (Currently Amended) The method of synthesis of the compound of claim 126 wherein the A-linked diarylketene comprises at least one of the formula

18a: R=OCH<sub>3</sub>

**18b:** R=O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> **18c:** R=(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

18d:  $R=N(CH_3)_2$ 

and A-B comprises at least one of the formula

÷

20a: R=OCH<sub>3</sub>

**20b:** R=O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> **20c:** R=(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> **20d:** R=N(CH<sub>3</sub>)<sub>2</sub>

128. (Currently Amended) The method of synthesis of the compound <u>according to any one</u> of claims 123 and 125 further comprising the step of reacting the B functionality with one nucleophilic species of a C functionality such as Foscarnet to form A-B-C.

129. (Currently .Amended) The method of synthesis of the compound of claim 105 comprising the general steps given by following representative formula

Serial No. 10/828,558 Page 87 of 125

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& &$$

**9a:** R=OCH<sub>3</sub>

**9b:** R=O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

9c:  $R = (CH_2)_3 CH_3$ 

10a: R=OCH<sub>3</sub> 10b: R=O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

10c:  $R = (CH_2)_3 CH_3$ 

N-CH<sub>3</sub>

**11a:** R=OCH<sub>3</sub>

**11b:**  $R = O(CH_2)_3 CH_3$ 

11c:  $R = (CH_2)_3 CH_3$ 

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130. (Currently Amended) The method of synthesis of the compound of claim 105

comprising the general steps given by following representative formula

131. (Original) The method of synthesis of the compound of claim 1 wherein the A

functionality comprises a phthalhydrazide such as a luminol derivative and the B functionality comprises a triarylpolymethine photochromic dye wherein A is attached to aryl groups of B comprising the steps of

forming a diaryl ketone,

forming a diaryl ketene from the diaryl ketone,

forming a protected aminophthalhydrazide such as aminophthalimide or aminophthalic acid diester,

adding a hydrocarbon linker to the protected aminophthalhydrazide, and

attaching the protected aminophthalhydrazide through the molecular linker to the aryl groups of diarylketene to form the precursor aminophthalimide-linked diarylketene, and reacting according to at least one of

- (a) forming the A functionality from the precursor, and condensing the A-linked diarylketene with an aryl alkene aldehyde to form A-B, and
- (b) condensing the precursor aminophthalimide-linked diarylketene with an aryl alkene aldehyde to form A precursor linked to B, and

forming the A functionality from the A precursor to form A-B.

- 132. (Original) The method of synthesis of the compound of claim 131 wherein the diaryl ketone is formed by a classical Friedel-Crafts acylation between a benzoyl halide and aryl compound with a hydrocarbon linker having a leaving group.
- 133. (Original) The method of synthesis of the compound of claim 132 wherein the aryl compound with a hydrocarbon linker having a leaving group comprises at least one of a halogenated-alkyl-aryl ether and a halogenated-aklyl-aryl amine wherein the halogen is the leaving group.
- 134. (Original) The method of synthesis of the compound of claim 133 wherein the halogenated-alkyl-aryl ether comprises 2-bromoethoxybenzene to give an aryl ketone such as 4-(2-bromoethoxy)benzophenone.
- 135. (Original) The method of synthesis of the compound of claim 133 wherein the halogenated-aklyl-aryl amine comprises 2-bromoethyl aminobenzene to give an aryl ketone such as 4-(2-bromoethyl amino)benzophenone.
- 136. (Original) The method of synthesis of the compound of claim 131 wherein the diaryl

ketone is converted to the corresponding diarylketene by reacting with a methylating reagent such as a methyl Grignard reagent, methyl lithium reagent, lithium dimethylcopper reagent and then dehydration with acid.

- 137. (Original) The method of synthesis of the compound of claim 136 wherein the diaryl ketone is converted to the corresponding diarylketene by reacting with methylmagnesium bromide and then dehydration with acid.
- 138. (Original) The method of synthesis of the compound of claim 131 wherein the diaryl ketone is converted to the corresponding diarylketene by a Wittig reaction.
- 139. (Original) The method of synthesis of the compound of claim 131 wherein a linker is attached to the protected aminophthalhydrazide by a reaction of a nucleophilic group of the linker or protected aminophthalhydrazide with a leaving group of the linker or protected aminophthalhydrazide.
- 140. (Original) The method of synthesis of the compound of claim 131 wherein a linker is attached to the protected aminophthalhydrazide by reaction to form a bond between at least one of a nitrogen, oxygen, or carbon atom of the linker and at least one of a nitrogen, oxygen, or carbon atom of group of the protected aminophthalhydrazide by an addition or a substitution reaction of a leaving group.
- 141. (Original) The method of synthesis of the compound of claim 140 wherein a linker is attached to the protected aminophthalhydrazide by a substitution reaction of at least one of a halogen, tosylate group, ester group with a nitrogen, oxygen, or carbon atom.
- 142. (Original) The method of synthesis of the compound of claim 131 wherein attaching the protected aminophthalhydrazide through the molecular linker to one of the aryl groups of diarylketene to form the precursor aminophthalimide-linked diarylketene is by a reaction of a nucleophilic group of the linker or aryl group of diarylketene with a leaving group of the linker or aryl group of diarylketene.
- 143. (Original) The method of synthesis of the compound of claim 142 wherein a linker is attached to the aryl group of diarylketene by reaction to form a bond between at least one of a nitrogen, oxygen, or carbon atom of the linker and at least one of a nitrogen, oxygen, or carbon

atom of group of the protected aminophthalhydrazide by an addition or a substitution reaction of a leaving group.

- 144. (Original) The method of synthesis of the compound of claim 143 wherein a linker is attached to the aryl group of diarylketene by a substitution reaction of at least one of a halogen, tosylate group, ester group with a nitrogen, oxygen, or carbon atom.
- 145. (Original) The method of synthesis of the compound of claim 131 wherein the precursor aminophthalimide-linked diarylketene is further reacted by condensation with an aryl alkene aldehyde in a nonaqueous solvent, containing an acid catalyst to form B linked to the A precursor.
- 146. (Original) The method of synthesis of the compound of claim 145 wherein the precursor aminophthalimide-linked diarylketene is an aminophthalimide-substituted 1,1-diarylethene,

the aryl alkene aldehyde is a p-aminophenyl alkene aldehyde such as p-(dimethylamino)-cinnamaldehyde,

the nonaqueous solvent is acetic anhydride,

the acid catalyst is at least one of perchloric acid and tetrafluoroboric acid, and

the B linked to the A precursor comprises a aminophthalimide-substituted multiarylpolymethine dye.

147. (Currently Amended) The method of synthesis of the compound of claim 145 wherein the precursor aminophthalimide-linked diarylketene comprises at least one of the formula

**3a**:  $R = N(CH_3)_2$ 

**3b**: R = H

 $3c: R = OCH_3$ 

**3d**:  $R = O(CH_2)_3CH_3$ 

**3e**:  $R = (CH_2)_3 CH_3$ 

the aryl alkene aldehyde has the formula

Serial No. 10/828,558 Page 94 of 125

4-(Dimethylamino)cinnamaldehyde, and

the precursor of A-B comprises at least one of the formula

**22b**: R = H **22c**: R = OCH<sub>3</sub>

**22d**: R =  $O(CH_2)_3CH_3$ **22e**: R =  $(CH_2)_3CH_3$ 

- 148. (Original) The method of synthesis of the compound of claim 145 wherein the phthalimide moiety of the A precursor is converted to the phthalhydrazide A functionality by treating with hydrazine, forming A-B.
- 149. (Original) The method of synthesis of the compound of claims 148 wherein the B functionality is protected by reacting with an anion such as hydroxide, methoxide and amine, the A-B precursor is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent in inert atmosphere and then treated with acid such as perchloric acid, tetrafluroboric acid to form A-B.
- 150. (Original) The method of synthesis of the compound of claim 131 wherein the phthalimide moiety of the A precursor of the precursor aminophthalimide-linked diarylketene is converted to the phthalhydrazide A functionality by treating with hydrazine, forming A attached to a B precursor.
- 151. (Original) The method of synthesis of the compound of claim 150 wherein the A-linked diarylketene is further reacted by condensation with an aryl alkene aldehyde in a nonaqueous

solvent, containing an acid catalyst to form A-B.

152. (Original) The method of synthesis of the compound of claim 151 wherein the A-linked diarylketene is an aminophthalhydrazide-substituted 1,1-diarylethene,

the aryl alkene aldehyde is a p-aminophenyl alkene aldehyde such as p-(dimethylamino)-cinnamaldehyde,

the nonaqueous solvent is acetic anhydride,

the acid catalyst is at least one of perchloric acid and tetrafluoroboric acid, and

A-B comprises a aminophthalhydrazide-substituted multiarylpolymethine dye.

153. (Currently Amended) The method of synthesis of the compound of claim 152 wherein the A-linked diarylketene comprises at least one of the formula

3a:  $R = N(CH_3)_2$ 

3b: R = H

 $3c: R = OCH_3$ 

**3d**: R =  $O(CH_2)_3CH_3$ 

**3e**: R =  $(CH_2)_3CH_3$ 

the aryl alkene aldehyde has the formula

4-(Dimethylamino)cinnamaldehyde, and

A-B comprises at least one of the formula

Serial No. 10/828,558 Page 96 of 125

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- 154. (Currently Amended) The method of synthesis of the compound <u>according to any one</u> of claims 149 and 151 further comprising the step of reacting the B functionality with one nucleophilic species of a C functionality such as Foscarnet to form A-B-C.
- 155. (Currently Amended) The method of synthesis of the compound of claim 131 comprising the general steps given by following representative formula

Serial No. 10/828,558 Page 97 of 125

**3a**:  $R = N(CH_3)_2$ 

3b: R = H

**3c**: R = OCH<sub>3</sub>

**3d**: R =  $O(CH_2)_3CH_3$ **3e**: R =  $(CH_2)_3CH_3$ 

**22d**: R = O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> **22e**: R = (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

**23a**:  $R = N(CH_3)_2$ 

23b: R = H

**23c**: R = OCH<sub>3</sub>

**23d**:  $R = O(CH_2)_3CH_3$ **23e**:  $R = (CH_2)_3CH_3$  24a: R = N(CH<sub>3</sub>)<sub>2</sub> 24b: R = H 24c: R = OCH<sub>3</sub> 24d: R = O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> 24e: R = (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

156. (Original) The method of synthesis of the compound of claim 131 comprising the

Serial No. 10/828,558 Page 99 of 125

general steps given by following representative formula

Serial No. 10/828,558 Page 100 of 125

$$R = CH_2$$

$$R = CH_2$$

$$R = CH_2$$

$$R = CH_2$$

$$R = R$$

3b: R = H

 $3c: R = OCH_3$ 

**3d**:  $R = O(CH_2)_3CH_3$ **3e**:  $R = (CH_2)_3CH_3$ 

**23a**:  $R = N(CH_3)_2$ 

23b: R = H

23c: R = OCH<sub>3</sub> 23d: R = O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> 23e: R = (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

**24a**:  $R = N(CH_3)_2$ 

**24b**: R = H

**24c**: R = OCH<sub>3</sub>

**24d**: R =  $O(CH_2)_3CH_3$ **24e**: R =  $(CH_2)_3CH_3$ 

$$\begin{array}{c} -N \\ -N \\ -N \\ -N \\ \end{array}$$

$$\begin{array}{c} Ethanol, H_2NNH_2 \\ reflux \\ \end{array}$$

$$\begin{array}{c} -N \\ +N \\ +N \\ \end{array}$$

$$\begin{array}{c} -N \\ +N \\ +N \\ \end{array}$$

157. (Original) The method of synthesis of the compound of claim 1 wherein the A

Serial No. 10/828,558 Page 102 of 125

functionality comprises a phthalhydrazide such as a luminol derivative and the B functionality comprises a triarylpolymethine photochromic dye wherein A is attached to aryl groups of B comprising the steps of

forming a diaryl ketone,

forming a diaryl ketene from the diaryl ketone,

condensing the diarylketene with an aryl alkene aldehyde to form B

forming a protected aminophthalhydrazide such as aminophthalimide or aminophthalic acid diester,

adding a hydrocarbon linker to the protected aminophthalhydrazide, and

attaching the protected aminophthalhydrazide through the molecular linker to the aryl groups of B to form the precursor aminophthalimide-linked B, and

forming the A functionality from the precursor to form A-B.

- 158. (Original) The method of synthesis of the compound of claim 157 wherein at least one of the diaryl ketone and diarylketene is halo-substituted and the protected aminophthalhydrazide is attached through the linker by an amination reaction.
- 159. (Original) The method of synthesis of the compound of claim 158 wherein the halosubstituted diarylketene precursor compounds comprises the formula of at least one of

**2a**:  $R = N(CH_3)_2$ 

2b: R = H

2c: R = OCH<sub>3</sub>

**2d**:  $R = O(CH_2)_3CH_3$ 

**2e**:  $R = (CH_2)_3CH_3$  and

the halo-substituted multiarylpolymethine dyes, such as 1-(p-bromophenyl)-1,5-bis(p-dimethylaminophenyl)-pentadienium perchlorate, are be prepared by condensation with a p-aminophenyl alkene aldehyde such as p-(dimethylamino)cinnamaldehyde.

160. (Original) The method of synthesis of the compound of claim 158 wherein B is protected by reacting with an anion such as alkoxide and then coupled with A by amination of aryl halide such as the palladium-catalyzed amination of aryl halide to obtain the alkoxide-protected aminophthalimide-substituted multiarylpolymethine dye.

161. (Currently Amened) The method of synthesis of the compound of claim 160 wherein the protected aminophthalhydrazide-linked to B from the alkoxide-protected aminophthalimide-substituted multiarylpolymethine dye comprises at least one of the formula

- 162. (Original) The method of synthesis of the compound of claim 160 wherein the alkoxide-protected aminophthalimide-substituted multiarylpolymethine dye is refluxed with hydrazine in a suitable solvent such as an alcoholic solvent to convert the amino-phthalimide moiety to the aminophthalhydrazide moiety and then treated with acid to generate A-B.
- 163. (Currently Amended) The method of synthesis of the compound of claim 162 wherein A-B comprises at least one of the formula

23a:  $R = N(CH_3)_2$ 

23b: R = H

**23c**: R = OCH<sub>3</sub>

**23d**: R =  $O(CH_2)_3CH_3$ **23e**: R =  $(CH_2)_3CH_3$ 

164. (Original) The method of synthesis of the compound of claim 162 further comprising the step of reacting the B functionality with one nucleophilic species of a C functionality such as Foscarnet to form A-B-C.

Serial No. 10/828,558 Page 104 of 125

- 165. (Original) The method of synthesis of the compound of claim 157 wherein at least one of the diaryl ketone and diarylketene is halo-substituted and an aminophthalhydrazide is attached through the linker by an amination reaction.
- 166. (Currently Amended) The A method of synthesis of a the compound of claim 1 having the formula A-B-C

where A is a chemiluminescent moiety;

B is an energy acceptor moiety, and

C is a biologically active moiety;

wherein the <u>chemiluminescent moiety</u> A <u>functionality</u> comprises an active oxalate and the <u>energy acceptor moiety</u> B <u>functionality</u> comprises a multiarylpolymethine photochromic dye wherein <u>the chemiluminescent moiety</u> A is attached to aryl groups of <u>the energy acceptor moiety</u> B comprising the steps of

forming a halo-substituted diaryl ketone,

forming a halo-substituted diaryl ketene from the diaryl ketone,

amination of the halo-substituted diaryl ketene to give amino diarylketene,

substitution at the amino group of the ketene to forming the corresponding sulfonamide,

condensing the sulfonamide with a catalyst, and

react with oxalyl halide to form A-B.

167. (Currently Amended) The A method of synthesis of a the compound of claim 1 having the formula A-B-C

where A is a chemiluminescent moiety;

B is an energy acceptor moiety, and

C is a biologically active moiety;

wherein the <u>chemiluminescent moiety</u> A <u>functionality</u> comprises an cyclized active oxalate and the <u>energy acceptor moiety</u> B <u>functionality</u> comprises a multiarylpolymethine photochromic dye wherein <u>the chemiluminescent moiety</u> A is attached to aryl groups of <u>the energy acceptor moiety</u> B comprising the steps of

forming a halo-substituted diaryl ketone,

forming a halo-substituted diaryl ketene from the diaryl ketone.

amination of the halo-substituted diaryl ketene to give amino diarylketene,

substitution at the amino group of the ketene to forming the corresponding sulfonamide,

reacting 2 molar proportions of a N-substituted aminodiarylketene with 1 molar oxalyl

Serial No. 10/828,558 Page 105 of 125

halide to yield the N,N'-bisaryl oxamide, <u>and</u> condensing the oxamide with a catalyst to form A-B.

- 168. (Original) The method of synthesis of the compound of claim 167 wherein the halosubstituted diaryl ketene is aminated using methods such as the palladium-catalyzed amination of aryl halide with benzophenoneimine to give the amino diarylketene.
- 169. (Original) The method of synthesis of the compound of claim 167 wherein the amino groups of the ketene are substituted forming the corresponding sulfonamide by reacting with sulfonyl anhydride.
- 170. (Original) The method of synthesis of the compound of claim 167 wherein the oxamide is condensed with an orthoester such as triethylorthofomate in a nonaqueous solvent such as acetic anhydride containing acid catalyst such as tetrafluoroboric acid, to form the cyclized oxamido-tetraarylpolymethine dye comprising A-B.
- 171. (Original) The method of synthesis of the compound of claim 166 further comprising the step of reacting the B functionality with one nucleophilic species of a C functionality such as Foscarnet to form A-B-C.
- 172. (Currently Amended) The method of synthesis of the compound of claim 167 wherein the general steps are given by following representative formula

173. (Currently Amended) The method of synthesis of the compound of claim 1 wherein the

chemiluminescent moiety A functionality comprises an active oxalate and the energy acceptor moiety B functionality comprises a multiarylpolymethine photochromic dye wherein the chemiluminescent moiety A is attached to aryl groups of the energy acceptor moiety B through a molecular linker comprising the steps of

forming B comprising a functionalized tetraarylpolymethine dye,

reacting a substituted amine with a sulfonyl anhydride to form a substituted alkyl sulfonamide,

reacting the substituted alkyl sulfonamide with an oxalyl derivative to form a substituted oxamide,

reacting the substituted oxamide with the functionalized tetraarylpolymethine dye to form A-B comprising a cyclized oxamido-tetraarylpolymethine.

- 174. (Original) The method of synthesis of the compound of claim 173 wherein the substituted amine is N-2-bromoethylsulfamide.
- 175. (Original) The method of synthesis of the compound of claim 173 wherein the oxalyl derivative is oxalyl chloride.
- 176. (Original) The method of synthesis of the compound of claim 173 wherein the oxamide is a N-2-bromoethyl-N-sulfonyloxamide derivative.
- 177. (Canceled)
- 178. (Original) The method of synthesis of the compound of claim 173 wherein the functionalized tetraarylpolymethine derivative is a salt of a 1,5-bis(4-hydroxyphenyl)-1,5-diarylpentadiene derivative.
- 179. (Original) The method of synthesis of the compound of claim 173 wherein the cyclized oxamido-tetraarylpolymethine A-B compound is a 1,5-(4,4'-(2,2'-N,N'-disulfonyloxamidodiethoxy)phenyl-1,5-diarylpentadiene cation derivative.
- 180. (Original) The method of synthesis of the compound of claim 173 further comprising the step of reacting the B functionality with one nucleophilic species of a C functionality such as Foscarnet to form A-B-C.

Serial No. 10/828,558 Page 108 of 125

181. (Currently Amended) The method of synthesis of the compound of claim 173 comprising the general steps given by following representative formula

Serial No. 10/828,558 Page 109 of 125

$$H_3CO$$
 $CI + H_2N$ 
 $H_3CO$ 
 $H_3CO$ 
 $H_3CO$ 

2 Br NHSO<sub>2</sub>CF<sub>3</sub> + Cr Cl CH<sub>2</sub>Cl<sub>2</sub> Br Br 
$$\frac{1}{8}$$
CO<sub>2</sub>S  $\frac{1}{8}$ N  $\frac{1}{8}$ SO<sub>2</sub>CF<sub>3</sub>

Claims 182-227 (Cancelled)

228. (New) The method of synthesis of the compound of claim 10 wherein the C moiety is at least one or a derivative or analog of one of the group of

prostaglandins

prostaglandin  $A_1$   $A_2$   $B_1$   $E_1$ ,  $E_2$  or an analog which possesses a vasodilatory effect on coronary arteries and other human vascular beds

prostaglandin E, F, A or an analog which possesses a positive cardiac inotropic effect prostaglandin A, E, or an analogue prostaglandin which possesses natriuretic and diuretic activity

prostaglandin A, G, E<sub>1</sub>, E<sub>2</sub> or an analogue such as 15(S)-15-methyl PGE 2 methylester, 16,16-dimethyl PGE2, AY-22,093, AY22,469, AY-22,443, or 15(R)-15-methyl PGE2 which inhibits gastric acid secretion

prostaglandin  $D_2$ ,  $E_1$  or an analogue which inhibits platelet aggregation prostaglandin  $E_1$ ,  $E_2$  or an analogue which causes bronchial dilatation prostaglandin  $F_2$  or an analogue which causes abortion by luteolysis prostaglandin  $A_2$ ,  $E_1$ ,  $E_2$ , or an analogue which induces erythropoiesis

prostaglandin E or an analogue which modulates T lymphocytes to decrease their ability to reject an allogenic graft

2'-isopropyl-4'-(trimethylammonium chloride)-5'-methylphenyl piperidine -1-carboxylate (Amo 1618) or an analog which inhibits the cyclization of trans-geranyl-geranyl-PP to copalyl-PP during Kaurene synthesis

adenosine cyclic 3', 5'-monophosphate or an analogue which inhibits the release and formation of phlogistic mediators such as histamine and kinins

4'-sulfamylphenyl

2-azo -7-acetamid-1-hydroxynaphthalene-3,6-disulfonate (Neoprontosil), 4'-sulfamyl-2, 4-diaminoazobenzene (Prontosil), or 5-(p-sulfamylphenylazo) salicylic acid (Lutazol) or analog which possess potent carbonic acid anhydrase inhibition

analogue of S-adenosyl homocysteine or sinefungin

phosphoglycolohydroxamate which inhibits Class II aldolases present in bacterial and fungi and is noninhibitory of Class I aldolases present in animals,

inosine analogue such as formycin B which inhibits nucleotide phosphorylase during nucleotide metabolism

phosphonoformate (Foscarnet) or an analog which inhibits the HIV reverse transcriptase enzyme

 $\gamma$ -amino-butyric acid (GABA) or an analog which is the major inhibitory neurotransmitter in the mannalian central nervous system

gabaculine, N-(5'-phosphopyridoxyl)-4-aminobutyric acid, ethanolamine-o-sulfate,  $\gamma$ -vinyl GABA, or  $\alpha$ -acetylenic GABA or an analog that is an inhibitor of the GABA-degrading enzyme, GABA: 2-oxoglutarate aminotransferase

Baclofen or a compound that inhibits GABA release

an oligonucleotide which binds to RNA or DNA and blocks transcription or translation of HIV or P-glycoprotein gene products adenosine which binds to brain purinergic receptors to suppress opiate withdrawal

adensoine whihe causes coronary vasodilatation

3-hydroxy-3-methylglutarate, 3-hydroxybutyrate, 3-hydroxy-3-methylpentanoate, 4-bromocrotonyl-CoA, but-3-ynoyl-CoA, pent -3-ynoyl-CoA, dec -3-ynoyl-CoA, ML-236A, ML-236B (compactin), ML-236C, mevinolin, mevinolinic acid, or a mevalonic acid analogue which is an inhibitor of 3-hydroxy -3-methylglutaryl-CoA reductase which catalyzes the rate-limiting and irreversible step of cholesterol synthesis where inhibition at this step does not lead to the accumulation of nonmetabolizable precursors

thioinosinate which suppresses T lymphocytes

Suramin, which is a powerful inhibitor of energy driven calcium uptake by the sarcoplasmic reticulum and is an intracellular inhibitor of Na+ K+ ATPase where both activities increase intracellular calcium concentrations with a concomitant inotropic effect

norepinephrine N-methyltransferase inhibitor such as 2,3-dichloro-α-methylbenzylamine, 2,3-dichlorobenzylamine, 2,3-dichlorobenzamidine, or 3,4-dichlorophenylacetamidine

adenosine cyclic 3', 5'-monophosphate or a cAMP analogue which blocks the synthesis of fatty acids and cholesterol in the liver is an antilipidemic agent,

an inhibitor of dihydroxyphenylalanine decarboxylase during the synthesis of epinephrine and norepinephrine such as psitectorigenin, genistein, 3', 4',5,7-tetrahydroxy-8-methylisoflavone, 8-hydroxygenistein, 3',5,7-trihydroxy-4',6-dimethylisoflavone, 3',5,7-trihydroxy-4',8dimethoxyisoflavone, D,L-B-(5-hydroxy-3-indolyl)-α-hydrazinopropionic acid, D.L-αhydrazino-α-methyldopa, D,L-B-(3-indolyl), -α-hydrazinopropionic acid, a derivative of phenylalanine such as N-methyl-3,4-dopa, α-acetamido-3,4-dimethyoxycinnamic acid, DL-αmethyl-3,4-dopa, α-methyl-B-(3-hydroxy-4-methoxyphenyl)alanine, α-methyl-3,4dimethoxyphenylalanine, or d-catechin; D,L-B-(3- indolyl)- $\alpha$ -methyl- $\alpha$ -hydrazinopropionic acid (R)-3,3,4-dihydroxyphenyl-1-fluoropropylamine, (S)- $\alpha$ -fluoromethyldopa,  $(S)-\alpha$ fluoromethyltyrosine, 5-(3,4-dihydroxycinnamoyl) salicylic acid, 3-hydroxycinnamic acid, caffeic acid, 3-mercaptocinnamic acid,  $\alpha$ -methyl-3-hydroxycinnamic acid,  $\alpha$ -ethyl-3hydroxycinnamic acid, 3-hydroxy-w-nitrostyrene, 3,4-dihydroxyhydrocinnamic acid. hydroxybenzalacetone, 3-hydroxybenzal furanyl ketone, 3-hydroxybenzal thiophenyl ketone, 3',4'-dihydroxyflavone, 8-O-glucoseflavone, flavone, 3-hydroxyphenyl pyruvic acid, 3,4-dihydroxyphenylpyruvic acid phenylthiopyruvic acid, 4-hydroxyphenylpyruvic acid, dithiosalicyclic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-7-sulfo-2-naphtholic acid, 3.5dihydroxy-2-naphtholic acid, 4-chlorocinnamic acid, 2-chlorocinnamic acid, 2,4dichlorocinnamic acid, 3-nitrocinnamic acid, 3,5-dibromo-2-hydroxycinnamic acid, 2,4,6-triiodo -3-hydroxycinnamic acid, 2-hydroxy-4'-cyanochalone, 4-(4-hydroxycinnamoyl) benzylnitrile, 2-(4-hydroxycinnamoyl)-1,4-dihydroxybenzene, quercetin-6'-sulfonic acid, 5-(2-hydroxy-3,5dibromocinnamoyl) salicylic acid or 5-(3-hydroxycinnamoyl) salicylic acid

an inhibitor of acrosin, a proteolytic enzyme located in the acrosome of sperm, such as tosyl lysine chloromethyl ketone, N- $\alpha$ -tosyl-L-arginine chloromethyl ketone, or ethyl p-guanidinobenzoate,

adenosine cyclic 3',5'-monophosphate (cAMP), N<sup>6</sup>, O<sub>2</sub> -dibutyryladenosine cyclic 3',5'-monophosphate or an analogue which produces an inotropic response,

adenosine kinase enzyme inhibitor such as 6,6'-dithiobis (9-B-D-ribofuranosylpurine), inhibitor of monoamine oxidase such as phenylhydrazine, phenylethylidenehydrazine, isopropyihydrazine, or iproniazid,

an inhibitor of catechol-o-methyltrasferase such as 3,5-diiodo-4-hydroxybenzoic acid, S-3'-deoxyadenosylL-homocysteine, pyrogallol, R04-4602, gallic acid, 3,5-dihydroxy-4methylbenzoic acid, 1,3-dihydroxy-2-methoxybenzene, 1-hydroxy-2,3-dimethoxybenzene, 2hydroxy-1,3-dimethoxybenzene, 1,3-dihydroxy-4-methoxybenzene, catechol. 3,4dihydroxybenzoic acid, caffeic acid, 5,6-dihydroxyindole, noradnamine, dopacetamide, H 22/54, quercetin, nordihydroguaiaretic acid, U-0521, arterenone, methylspinazarin, MK 486, dopa, papaveroline, isoprenaline, 7,8-dihydroxy-chlorpromazine, 3-hydroxy-4-pyridone, tetrahydroisoquinoline pyridoxal 5'-phosphate, iodoacetic acid, 3-mercaptotyramine, dehydrodicaffeic acid dilactone, methylspinazorin, 3',5,7-trihydroxy-4',6-dimeth-oxyisoflavone, 3',5,7-trihydroxy-4',8dimeth-oxyisoflavone, 6,7-dihydromethylspinazarin, S-adenosylhomocysteine, Stubercidinylhomocysteine, 3',8-dihydroxy-4',6,7-trimethoxyisoflavone,7-O-methylspinochrome B, 6-(3-hydroxybutyl)-7-O-methylspinachrome B, 3,5-diiodosalicyclic acid, or pyridoxal-5'phosphate,

an inhibitor of adenosine deaminase which blocks the metabolism of adenosine such as coformycin, arabinosyl-6-thiopurine, 6-methylthioinosine, 6-thioinosine, 6-thioguanosine,  $N_1$ -methyladenosine,  $N_6$ -methyladenosine, 2-fluorodeoxyadenosine, 2-fluoroadenosine, inosine, 2'-deoxyinosine, deoxycoformycin, 1,6-dihydro-6-hydroxymethyl purine ribonucleoside, erythro-9-

(2-hydroxy-3-nonyl)adenine, or 9-B-D-arabinofuranosyl-6-hydroxylaminopurine,

an inhibitor of adenylate kinase, 5'-nucleotidase, and adenosine translocase such as  $p^1$   $p^5$  -diadenosine pentaphosphate,  $\alpha,\beta$ -methylene adenosine diphosphate, and nitrobenzyl-6-thioinosine, respectively,

an inhibitor of γ-aminobutyric acid uptake such as D,L-2,4-diaminobutyric acid, D,L-B-hydroxy GABA, (-)-nipecotic acid, trans-4-aminocrotonic acid, cis-3-aminocyclopentane-1-carboxylic acid, trans-3-aminocyclopentane-1-carboxylic acid, B-guanidinopropionic acid, homohypotaurine, 4-aminopentanoic acid, homotaurine, B-alanine, imidazoleacetic acid, 6-aminohexanoic acid, D,L-carnitine, D,L-2,6-diaminopimetic acid, D,L-2-fluoro GABA, guanidino acetic acid, 2-hydrazinopropionic acid, taurine, D,L-ornithine, or sulphanilamine which potentiates the inhibitory action of GABA,

inositol 1,4,5-triphosphate,

guanosine 5' cyclic monophosphate or 8-bromo guanosine 5' cyclic monophosphate which relaxes smooth muscle,

an inhibitor of the uptake system for glycine, the inhibitory synaptic transmitter of the spinal cord, such as hydrazinoacetic acid,

isoquinoline-sulfonamide inhibitor of protein kinase C, cAMP-dependant protein kinase, or cGMP-dependent protein kinase such as N-(2-aminoethyl)-5-isoquino-linesulfonamide,

Ribavirin which is active against HSV-1 and 2, hepatitis, and influenza viruses, or phosphonoacetic acid which is a highly specific inhibitor of Herpes Simplex virus induced polymerase and is active against HSV-1 and HSV-2, or adenine arabinoside (ara-A), cytosine arabinoside (Ara-C), ara-A 5'-monophosphate (ara-AMP), or hypoxanthine arabinoside (ara-Hx) which is active against HSV or phagicin which is active against vaccinia and HSV, or 4-fluoroimidazole, 4-fluoroimidazole-5-carboxylic acid, 4-fluoroimidazole-5-carboxamide, 5-fluoro-1-B-D-ribofurano-sylimidazole-4-carboxamide, 5-amino-1-B-D-ribofuranosylimidazole-4-carboxamide, poly (I), poly (C), sinefungin, iododeoxyuridine, 9-(2-hydroxy-ethoxymethyl) guanine, gliotoxin, distamycin A, netropsin, congocidine, cordycepin, 1-B-D-arabinofuranosylthymine, 5,6-di-hydroxy-5-azathymidine, pyrazofurin, toyocamycin, or tunicamycin,

an inhibitor of fungal chitin synthetase such as polyoxin D, nikko-mycin Z, or nikkomycin X,

an impermeant antifungal agent such as ezomycin A<sub>1</sub>, A<sub>2</sub>, B<sub>1</sub>, B<sub>2</sub>, C<sub>1</sub>, C<sub>2</sub>, D<sub>1</sub>, or D<sub>2</sub> or platenocidin, septacidin, sinefungin, A9145A, A9145C, or thraustomycin,

an inhibitor of central nervous system carbonic anhydrase such as methazolamide, or 2-benzoylimino-3-methyl- $\Delta^4$  -1,3,4-thiadiazoline-5-sulfonamide subsgituted at the benzolyl group

with 3,4,5-trimethoxy, 2,4,6-trimethoxy, 2,4,5-trimethoxy, 4-chloro, 4-bromo, 4-iodo, or hydrogen,

an inhibitor of dopamine-B-hydroxylase during the synthesis of norepinephrine and epinephrine such as fuscaric acid, 5-(3',4'-dibromobutyl)picolinic acid, 5-(3'-bromobutyl) picolinic acid. 5-(3',4'-dichlorobutylpicolinic acid. YP-279, benxyloxyamine, hydroxybenzyloxyamine, U-21,179, U-7231, U-6324, U-0228, U-5227, U-10,631, U-10,157, U-1238, U-19,963, U-19,461, U-6628, U-20,757, U-19,440, U-15,957, U-7130, U-14,624, U-22,996, U-15,030, U-19,571, U-18,305, U-17,086, U-7726, dimethyldithiocarbamate, diethyldithiocarbamate. ethyldithiocarbamate, 2-mercaptoethylguanidine, thiophenol, mercaptoethylamine, 3-mercaptopropylguanidine, 3-mercap- toprbpyl-N-methylguanidine, 2mercaptoethanol, 2-mercaptoethyl-N-methylguanidine, 2-mercaptoethyl-N,N'dimethylguanidine, 4,4,6-trimethyl-3,4-dihydropyrimidine-2-thiol, N-phenyl-N'-3-(4H-1,2,4trizolyl)thiourea, methylspinazarin, 6,7-dimethylspinazarin, 7-O-methy-spinochrome B, 6-(3hydroxybutyl)-7-O-methylspinachrome B, aquayamycin, chrothiomycin, frenoclicin, N-n-butyl-N'-3-(4H-1,2,4-trazolyl) thiourea, propylthiouracil, mimosine, mimosinamine, or mimosinic acid,

an inhibitor of histidine decarboxylation during the synthesis of histamine such as 2 hydroxy-5-carbomethoxybenzyloxyamine, 4-toluene-sulfonic acid hydrazide. 3-hvdroxv benzyloxyamine, hydroxylamine, aminooxyacetic acid, 4bromo-3-hydroxybenzyloxyamine (NSD-1055), rhodanine substituted in the 3 position with p-chlorophenethyl, p-chlorobenzyl, pmethylthiobenzyl, p-methylbenzyl, p-fluorobenzyl, amino, 3,4-dichlorobenzyl, p-bromobenzyl, p-methoxybenzyl, p-bromoanilino, p-iodoanilino, p-chloroanilino, p-toluidino, anilino, 2.5dichloroanilino, dimethylamino, or p-methoxyphenyl; 2-mercaptobenzimidazole-1,3-dimethylol, 4-bromo-3-hydroxy -benzoic acid, 4-bromo-3-hydroxybenzyl alcohol, 4-bromo-3-hydroxyhippuric acid, (R,S)-α-fluoromethyl- histidine, (S)-α-fluoromethylester, L-histidine ethyl ester, L-histidinamide. D,L-3-amino-4-(4-imidazolyl)-2-butanone, 2-bromo-3hydroxybenzyloxyamine, 5-bromo-3-hydroxybenzyloxyamine, 4,6-dibromo-3hydroxybenzyloxyamine, aminooxypropionic acid, benzyloxyamine. 4-bromo-3benzenesulfonyloxybenzyloxyamine, 3',5,7-trihydroxy-4',6-dimethoxyisoflavone, lecanoric acid, N-(2,4-dihydroxybenzoyl)-4-aminosalicylic acid, or 3',5,7-trihydroxy-4',8-dimethoxyisoflavone.

an pharamaceutical aget of drug that appear in Physicians Desk Reference, Edward R. Barnhart, 41th ed., 1987, Medical Economics Company Inc., N.J.; USAN and the Dictionary of Drug Names, ed. by Mary C. Griffiths, The United States Pharmacopedial Convention, (1986); and The Pharmacological Basis of Therapeutics, ed. by A.G. Gilman, L. Goodman, A. Gilman, 7th ed., (1985), MacMillan Publishing Co., N.Y., N.Y.,

a centrally acting converting enzyme inhibitor such as captopril,

an antibacterial agent such as penicillin, cephalosporin, or cephamycin, with  $\beta$ -lactamase resistance,

an agent which blocks bacterial synthesis of tetrahydrofolate such as a sulfonamide (an analogue of p-aminobenzoic acid) including sulfanilamide, sulfadiazine, sulfamethoxazole, sulfisoxazole, or sulfacetamide

an inhibitor of dihydrofolate reductace including pyrimethamine, cycloguanil, trimethoprin, isoaminopterin, 9-oxofolic acid, or isofolic acid,

a bactericidal agent such as nalidixic acid or oxolinic acid,

an inhibitor of bacterial protein synthesis such as vancomycin, an aminogylcoside, erythromycin, tetracyclin, or chloramphenicol,

an inhibitor of viral DNA polymerase such as vidarabine,

tuberculostatic or tuberculocidal agent such as isoniazid or aminosalicyclic acid,

an anthelmintic agent such as oxamniquine, piperazine, metronidazole, diethylcarbamazine, paromomycin, niclosamide, bithionol, metrifonate, hycanthone, dichlorophen, or niclosamide,

an H<sub>2</sub>-blocking agent such as cimetidine or ranitidine,

an agent which blocks release of norepinephrine such as sotalol, guanethidine, pindolol, pronethalol, KO 592, practolol, oxprenolol, or pronethalol,

a xanthine oxidase inhibitor such as allopurinol, thioinosinate, 5.7-dihydroxypyrazolo 1,5-pyrimidine substituted at the 3 position with hydrogen, nitro, bromo, chloro, phenyl, 3pyridyl, p-bromophenyl, p-chlorophenyl, p-acetylanilino, p-tolulyl, m-tolulyl, naphthyl, or 3,4methylenedioxyphenyl; 8-(m-bromoacetamidobenzylthio)hypoxanthine, 8-(mbromoacetamidobenzylthio)hypoxanthine, guanine substituted at the 9 position with phenyl, 4chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4dimethylaminophenyl, 4-aminophenyl, 3-aminophenyl, 3-trifluormethylphenyl, 4-benzamido, 4carboxylphenyl, 4-methylpheyl, 4-ethylphenyl, 3-methylphenyl, B-naphthyl, or 4-ethoxyphenyl; 4,6-dihydroxypyrazolo 3,4-d pyrimidine, 4-trifluoromethylimidazoles substituted at the 2 position with phenyl, p-chlorophenyl, p-methoxyphenyl, p-acetylanilino, p-nitrophenyl, pdimethylaminophenyl, p-cyanophenyl, p-fluorophenyl, p-carboxyphenyl, m-chlorophenyl, 3.4dichlorophenyl, 4-pyridyl, 3-pyridyl, 2-quinolyl, 6-quinolyl, 4-quinolyl, 7-quinolyl, 2-pyrazinyl, or 1-(2-pyridyl-4-trifluoromethyl-5-bromoimidazolyl; 5-(4-pyridyl)-1,2,4-triazoles substituted at the 5 position with 4-pyridyl, 3-pyridyl, 2-pyridyl, phenyl, p-chlorophenyl, m-chlorophenyl, psulfonamidophenyl, 3,5-dichlorophenyl, 3,5-dicarboxyphenyl, 6-quinolyl, 2-furyl, 4-pyridazinyl, 2-thienyl, 2-pyrimidinyl, 4-pyrimidinyl, or 4-pyrazinyl; difunisal, 4(or 5)-(2-aminoethylthioazo)imidazole-5(or 4)-carboxamide, 4 (or 5)-diazoimidazole-5(or 4)-carboxamide, or S-õ5(or

4)-carbamoyl-4(or 5)-imidazolyl azo cysteine,

an agent which inhibits DNA synthesis such as a bis-thiosemicarbazone, 3,5diisopropylsalicylhydroxamic acid. 4-hydroxybenzoylhydroxamic acid. 3methylsalicylhydroxamic acid 2,5-dihydroxybenzoylhydroxamic acid, or 2-hydroxy-3,4,5trimethoxybenzoylhydroxamic acid; or which inhibits nucleotide synthesis such as N-(phosphoacetyl)-L-aspartate which inhibits asparatate transcarbamylase during pyrimidine synthesis, or azaserine or 6-diazo-5-oxo-L-norleucine which inhibits purine synthesis at the phosphoribosyl-formyl-glycineamidine synthetase step; or which is an antifolate such as methotrexate, 2,4-diamino-5-benxyl-6-(4-phenylbutyl) pyrimidine, 2,4-diamino-5-phenyl-6-(4-phenylbutyl) phenylbutyl) pyrimidine, 2,4-diamino-5-phenyl-6-(3-anilinopropyl) pyrimidine, 2-amino-4hydroxy-5-phenyl-6-(3-p-aminobenzoylglutamic acid propyl) pyrimidine, N-(p-oo(2,4-diamino-6-quinazolinyl)methyl-methylaminobenzoyl-L-glutamic N-p-2,4-diamino-5acid. methylquinazolinyl)methylaminobenzoyl-L-aspartic acid. N-p-(2-amino-4-hydroxy-6quinazolinyl) methyl-methylamino benzoyl-L-glutamic acid, 2,4-diaminoquinazolines: CCNSC 105952, CCNSC 112846, CCNSC 121346, CCNSC 122761, CCNSC 122870, CCNSC 529859, CCNSC 529860, or CCNSC 529861; 8-aza GMP, 7-deaza-8-aza GMP, 2'-dGMP, B-Darabinosyl GMP, pentopyranine A-G, B-ribofuranosyl-1,3-oxazine-2,4-dione, pyrazofurin, 6-(pchloroacetylanilinomethyl)-5-cetylvinylanilinomethyl)-5-(p-chlorophen yl)-2.4-diaminopyridine. 6-(p-chloroacetylethylanilino-methyl)-5-(p-chlorophenyl)-2,4-diamino pyridine, 6-(pchlorophenylbutylanilinomethyl)-5-(p-chlorophenyl)-2,4-diamino pyridine, p-(2,6-diamino-1,2dihydro-2, 2-dimethyl- S-triazin-1-yl) phenylpropionyl sulfanilylfluoride or variants of the propionamide bridge of acrylamido, N-ethylsulfonamido, N-ethylcaboxamido, oxyacetamido, or oxythyloxy; or which inhibits purine or pyrimidine synthesis such as xylosyladenine, 6azauridine, 5-aminouridine, 5-azaorotic acid; or which inhibits nucleotide interconversion such as hadacidin, 6-mercaptopurine, azathioprine, nitro-dUMP, psicofuranine, decoyinine, 5fluorouracil, 5-fluorodeoxyuridine, shadowmycin; or which inhibits nucleotide utilization such as cytosine arabinoside, arabinosyladenine; or which becomes incorporated into polynucleotides such as 8-azaguanine, tubercidine, toyocamycin, sangivamycin, formycin, 7-deazainosine, 8azainosine, or 7-thia-7, 9-dideazainosine; or which is a glyoxalase inhibitor such as Glyo-I, or Glyo-II,

an agent which blocks synthesis of prostaglandin  $A_2$  which effects platelett aggregation such as salicylic acid, pyrogallol, 5,8,11,14-eicosatetraynoic acid,  $\alpha$ -naphthol, guaiacol, propylgallate, nordihydroguiaretic acid, N-0164, benzydamine, 9,11-azoprosta-5, 13-dienoic acid, 2-isopropyl-3-nicotinylindole,

an agent which blocks prostaglandin synthetase such as indomethacin, sulindac, tolmetin,

mefenamic acid, ibuprofen, naprozen, fenoprofen, fluribiprofen, ketoprofen, meclofenamic acid, flufenamic acid, niflumic acid, benzydamine, oxyphenbutazone, asprin, acetaminophen, salicylamide, O-carboxydiphenylamine, tolectin, diclofenac, 2,7-dihydroxynaphthalene, 5-(4-chlorobenzoyl)-1-methylpyrrole-2-acetic acid, 5-(4-methylbenzoyl)-1,4-dimethylpyrrole-2-acetic acid, 5-(4-fluorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid, 5-(4-fluorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid, 5-(4-chlorobenzoyl)-1,4-dimethylpyrrole-2-(2-propionic acid), 5,6-dehydroarachidonate, 11,12-dehydroarachidonate, or 5,8,11,14-eicosatetraynoate; or of an agent which blocks lipoxygenase or blocks leukotriene action such as BW755C, FPL 55712, or U-60,257

an antiarrhythmic agent such as procainamide or quinidine,

an inhibitor of hepatic synthesis of Vitamin K dependent clotting factors such as warfarin sodium, dicumarol, 4-hydroxycoumarin, phenprocoumon, or acenocoumarol,

an agent which relaxes vascular smooth muscle such as hydralazine, minoxidil, or isoxsuprine,

Na<sup>+</sup> K<sup>+</sup> -ATPase inhibitor such as digtoxigenin, digoxigenin, cymarol, periplogenin, or strophanthidiol, or ouabain glycosides, cardenolides, or basic esters, or ICI-63,632, ICI-63,605, ICI-62-655, ICI-62,838, ICI-69,654, ICI-58,622, ICI-61,374, ICI-57,267, ICI-61,424, ICI-61,411, ICI-65,199, ICI-70,898, ICI-70,899, ICI-70,900, ICI-70,901, ICI-62,966, ICI-65,210, ICI-63,116, ICI-62,936, ICI-65,551, ICI-63,978, ICI-62,276, ICI-63,056, ICI-67,135, ICI-67,167, ICI-67,134, ICI-67,875, ICI-67,880, or ICI-61,558,

a calcium channel blocker such as prenylamine, verapamil, fendiline, gallopamil, cinnarizine, tiapamil, diltiazem, bencyclan, or nifedipine; or an agent which stabalizes calcium binding to cellular calcium stores and thereby inhibits the release of this calcium by contractile stimuli such as 8-(N,N-diethylamino)-octyl 3,4,5-trimethoxybenzoate (TMB-8),

a monoamine oxidase inhibitor such as tranylcypromine, phenylethylamine, transcinnamic acid, phenelzine, or isocarboxazid,

a benzodiazepine compound such as clorazepate, valproic acid,

an agent which causes repression of the synthesis of HMG-COA reductase such as 20- $\alpha$ -hydroxycholesterol, 22-ketocholesterol, 22- $\alpha$ -hydroxycholesterol, 25-hydroxycholesterol, 22- $\beta$ -hydroxycholesterol, 7- $\alpha$ -hydroxycholesterol, 7- $\beta$ -hydroxycholesterol, 7-ketocholesterol, or kryptogenin; or of an agent which inhibits HMG-COA reductase such as, lorelco; or of an agent which inhibits lipolysis such as 5-methylpyrazole -3-carboxylic acid (U-19425), nicotinic acid, uridine, inosine, 3,5-dimethylisoxazole (U-21221), 3,5-dimethypyrazole, prostaglandin  $E_2$ , eritadenine, or eritadenine isoamyl ester; or of an agent which inhibits lipogenesis such as

ascofuranone, (-)-hydroxycitrate, or tetrolyl-CoA; or of an agent which is hypocholesterolemic such as lentysine; or of an agent which lowers triglycerides such as lopid; or of an agent which is an inhibitor of acetyl-CoA carboxylase during lipogenesis such as 2-methyl -2-p-(1,2,3,4-tetrahydro-1-naphthyl)-phenoxy-propionate (SU13437), 2-(p-chlorophenoxy)-2-methylpropionate, kynurenate, xanthurenate, kynurenine, 3-hydroxyanthranilate, or 2-methyl-2-p-(p-chlorophenyl)phenoxypropionate; or of an agent which is an inhibitor of hepatic  $\beta$ -lipoprotein production such as orotic acid,

a vasodilater such as WS-1228A, or WS-1228B; or of an anti-inflammatory agent such as amicomacin A,

a protease inhibitor such as leupeptin; or which is an inhibitor of pepsin such as a pepstatin, a pepstanone, or a hydroxypepstatin,

an inhibitor of cell surface enzymes such as bestatin, amastatin, forphenicine, ebelactone, or forphenicin,

a phosphodiesterase inhibitor such as theophyllineacetic acid, theophylline, dyphylline, disodium cromoglycate, 6-n-butyl-2,8-dicarboxy-4,10-dioxo-1,4,7,10-tetrahydro-1,7-phenanthrolin, 2-chloroadenosine, dipyridamole, EG 626, AY-17,605, AY-17,611, AY-22,252, AY-22,241, cis-hinokiresinol, oxy-cis-hinokiresinol, tetrahydro-cis- hinokiresinol, transhinokiresinol, dehydrodicaffeic acid, 2,6,4'-trihydroxy-4-methoxybenzophenone, phydroxyphenyl crotonic acid, papaverine, 3-(5-tetrazolyl)-thioxanthone-10,10-dioxide, 3-carboxythioxanthone-10,10-dioxide, W-7, HA-558, MY-5445, OPC-3689, OPC-13135, or OPC-13013, reticulol, PDE-I, or PDE-II,

an inhibitor of tyrosine hydroxylase, the enzyme catalyzing the rate-limiting reaction in the biosynthesis of norepinephrine, such as azadopamine, isopropylazadopamine, dimethylazadopamine; triphenolic compounds such as n-propylgallate; diphenolic benzoic acid derivatives such as 3,4-dihydroxybenzoic acid; phenylcarbonyl derivatives such as 3,4dihydroxybenzaldehyde, arterenone, or adrenalone H 22/54, 3-iodo-L-tyrosine, D,L-α-methyl-ptyrosine, L-3-iodo-α-methyltyrosine, 3-bromo-α-methyltyrosine, gentistic acid, 3-chloro-αmethyltyrosine, phenylalanine derivatives, 3,5-diiodo- L-tyrosine, 3,5-dibromo-L-tyrosine, 3bromo-α-methyl-Ltyrosine, 3-fluro-α-methyl-L-tyrosine, catechol analogues, 3,4dihydroxyphenylethylacetamide, 3,4-dihydroxyphenylisoproplyacetamide, 3,4dihydroxyphenylbutylacetamide, 3,4-di-hydroxyphenylisobutylacetamide, D,L-amethylphenylalanine, D,L-3-iodophenylalanine, D,L-4-iodophenylalanine, D,L-α-methyl-3iodophenylalanine, D,L-a-methyl-3-bromophenylalanine, D,L-α-methyl-3-chlorophenylalanine, D,L-α-methyl-3-fluorophenylalanine, mimosine, mimosinamine, mimosinic 7-Omethylspinochrome В, 6-(3-hydroxybutyl)-7-O-methylspinachrome В, aquayamycin,

Serial No. 10/828,558 Page 120 of 125

chrothiomycin, frenolicin, fuscaric acid, pentylpicolinic acid, dopstatin, methylspinazarin, 6,7-dihydroxymethylspinazarin, 3-ethyl-α-methyltyrosine, 3-methyl-α-methyltyrosine, 3-isopropyl-x-methyltyrosine, 3-allyl-α-methyltyrosine, 3-4-hydroxy-3-(2-methylallyl)-phenyl-2-methylalanine, 3-3-(2,3-epoxypropyl)-4-hydroxyphenyl-2-methylalanine, 3-isobutyl-α-methyltyrosine, 3-methylvinyl-α-methyltyrosine, 5-methyl-6,7-diphenyltetrahydropterin, 3-(2,3-dihydro-2,2-dimethyl-5-benzofuranyl-2-methylalanine, 3-2,3-dihydro-2,2-dimethyl-5-benzofuranyl-2-methylalanine, α-methyldopa, or ethyl-3-amino-4H-pyrrolo 3,4-isoxazole carboxylate, and proteins including enzymes and hormones such as insulin, erythropoietin, interleuken 2, interferon, growth hormone, atrial natriuretic factor, tissue plasminogen activator.

229. (New) The method according to claim 1, wherein the phthalhydrazide comprises at least one selected from the group consisting of phthalimide, aminophthalic acid diester, aminophthalic acid dihydrazide, aminophthalic anhydride and phthalhydrazide protected by a hydrolyzable group.